

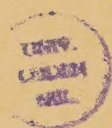
EPIDEMIOLOGICAL STUDIES IN MALIGNANT LYMPHOMA

with special reference to occupational exposure to
organic solvents and to reproductive factors

Håkan Olsson



Lund 1984

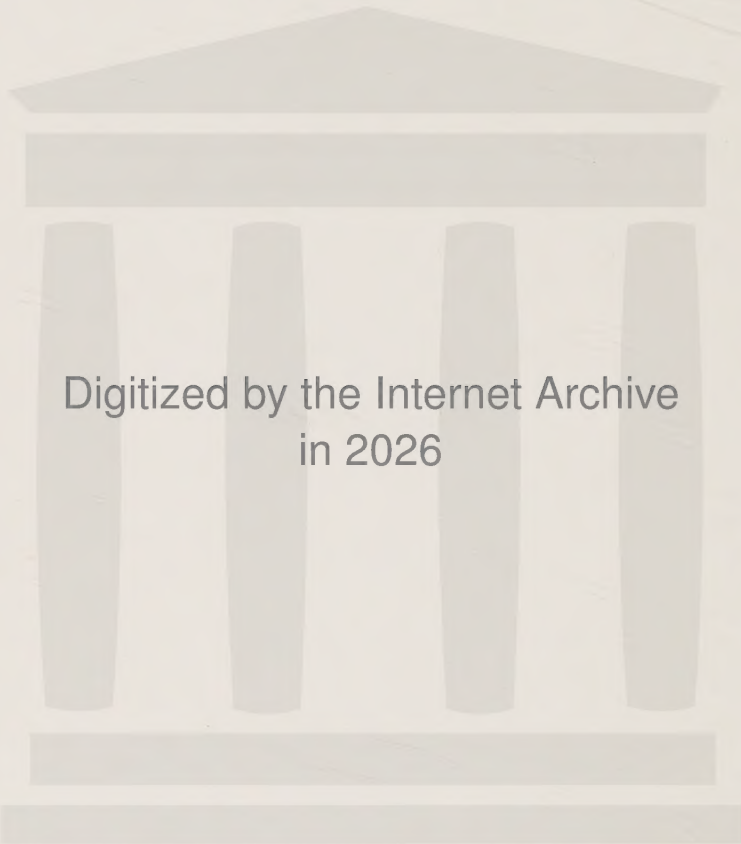


EPIDEMIOLOGICAL STUDIES IN MALIGNANT LYMPHOMA

**with special reference to occupational exposure to
organic solvents and to reproductive factors**

Håkan Olsson

Lund 1984



Digitized by the Internet Archive
in 2026

To Mona
Daniel, Ulrika, Olof

Apart from some unpublished results, the present work is based on the following papers, which will be referred to in the text by their Roman numerals.

- I. Occupational handling of chemicals preceding Hodgkin's disease in men. H. Olsson, L. Brandt. *Br Med J* 1979; 2: 580-581.
- II. Occupational exposure to organic solvents and Hodgkin's disease in men. A case-referent study. H. Olsson, L. Brandt. *Scand J Work Environ Health* 1980; 6: 302-305.
- III. Supradiaphragmatic presentation of non-Hodgkin's lymphoma in men occupationally exposed to organic solvents. H. Olsson, L. Brandt. *Acta Med Scand* 1981; 210: 415-418.
- IV. Impaired testicular function in a subgroup of men with malignant lymphoma. H. Olsson, L. Brandt, J. Ranstam, M. Bjerström. Submitted for publication.
- V. Low fertility prior to therapy in a subgroup of men with malignant lymphoma. H. Olsson, J. Ranstam. Submitted for publication.
- VI. Late age at first full term pregnancy as a risk factor for women with malignant lymphoma. H. Olsson, M. Landin Olsson, J. Ranstam. Submitted for publication.

ABBREVIATIONS

AFFP	age at first full term pregnancy
CI	confidence interval
HD	Hodgkin's disease
NHL	non-Hodgkin's lymphoma
P-testosterone	plasma testosterone
S-FSH	serum follicle-stimulating hormone
S-LH	serum luteinizing hormone

CONTENTS

INTRODUCTION	9
Risk factors	10
The rationale for studying exposure to organic solvents as a lymphoma risk factor	14
The rationale for studying sex hormones and reproductive factors in patients with malignant lymphoma	14
AIMS OF THE PRESENT INVESTIGATION	16
MATERIALS AND METHODS	17
RESULTS	23
DISCUSSION	29
General considerations	29
Papers I-III	31
Papers IV-VI	35
CONCLUDING REMARKS	40
ACKNOWLEDGEMENTS	42
REFERENCES	45

PAPERS I - VI

INTRODUCTION

Incidence of malignant lymphoma in relation to histology, sex and age

Malignant lymphoma is a rather uncommon group of tumours constituting 1044 new cases in 1980 in Sweden (Cancer Incidence in Sweden 1980). On clinical and pathologic grounds two main groups of malignant lymphoma are distinguished, Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The age-standardized incidence of HD in Sweden was in 1980 for males 3.1/100 000 and for females 2.3/100 000. For NHL the incidence was 11.2/100 000 and 7.4/100 000 respectively.

The age distribution of HD is bimodal with a post-pubertal incidence peak and a steady increase in incidence over 45 years of age (Mac Mahon, 1957, Grufferman, 1982). For NHL there are more cases with advancing age and no bimodality is evident (Greene, 1982). In Sweden there has been no increase in the incidence of HD during the last decade and there may actually have been a decline during the period 1976-1980 (Cancer Incidence in Sweden 1980). This is in contrast to NHL where a constant rise in incidence can be seen. A similar increase in NHL has been found in the United States and it has been proposed that this pattern may reflect the presence of uncontrolled environmental factors (Greene, 1982).

Geographic variations in incidence

Hodgkin's disease in childhood may be especially common in developing countries (Correa and O'Connor, 1971). In the United States a north to south declining gradient in HD mortality has been noted (Cole et al, 1968). Geographic variations may also occur in NHL. Thus different mortality rates have been described for coastal California and the midwest compared with the southeast of the United States (Cantor and Fraumeni, 1980).

In Sweden more cases of HD are diagnosed in the south-eastern and north-western parts of the country than in other areas (Cancer Incidence in Sweden 1978-1980). For NHL the highest incidence is found in the south and south-eastern parts of Sweden (Cancer Incidence in Sweden 1978-1980).

Socio-economic factors and incidence

It has been suggested that the risk of HD at a young age may be related to a high standard of living (Le Shan et al, 1959, Cohen et al, 1964, Gutensohn and Cole, 1977). It has also been proposed that the histopathological sub-



group nodular sclerosis is especially common in higher social groups (Henderson et al, 1979). In more recent studies no relation between social group and incidence of HD has been found (Registrar General, 1971, Registrar General, 1978). In Sweden there is no apparent relation between socio-economic status and incidence of HD in men over 25 years of age (Hardell and Bengtsson, 1983).

A positive association between a high standard of living, urban residence and a high incidence of NHL has been described (Registrar General, 1958, Guralnick, 1963, Hoover et al, 1975).

Prognosis

The prognosis of HD has greatly improved in later years. Approximately 70 per cent of the patients may be long-term survivors or cured (De Vita and Hellman, 1982). A smaller proportion of patients with NHL are cured (De Vita and Hellman, 1982). However, treatment often gives a substantial improvement in the quality of life for long periods (De Vita and Hellman, 1982).

Both for HD and NHL the side-effects and the late complications of the treatment are important factors (De Vita and Hellman, 1982). Investigations of risk factors should therefore be given a high priority in order to possibly provide means for prevention of the diseases.

Risk factors

Immunosuppression

Malignant lymphoma has been found to be unduly common in certain acquired or genetically determined immunodeficiency states (Louie et al, 1980). According to the Immunodeficiency-Cancer Registry, Gatti and Good (1971) estimated that primary immunodeficiency syndromes are associated with a 10 000-fold increased risk of developing malignant tumours, especially of the lymphoreticular system. Patients with X-linked recessive lymphoproliferative malignancy syndrome, severe combined immunodeficiency, the Wiskott-Aldrich syndrome, ataxia teleangiectasia, common variable immunodeficiency, IgA deficiency, IgM deficiency, and other genetically determined immunodeficiency syndromes are especially prone to develop malignant lymphoma and other lymphoreticular diseases (Louie et al, 1980). Defective immunoregulatory mechanisms together with recurrent infections and anti-

genic challenges may be responsible for the increased risk of lymphoma in this group of patients (Waldmann et al, 1972).

Recipients of renal and cardiac transplants are at an increased risk of developing malignant lymphoma, especially in the central nervous system (Fraumeni and Hoover, 1977, Kinlen et al, 1979, Anderson et al, 1978). A predominance of diffuse histiocytic lymphoma seems to be characteristic in these patients (Greene, 1982). Immunosuppressive agents together with graft-versus-host allogenic stimulation may activate virus-induced lymphoproliferation, which may later evolve into malignant lymphoma (Schwartz, 1972, Matas et al, 1975).

Patients with autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus and sarcoidosis run an increased risk of malignant lymphoma (Louie and Schwartz, 1978, Brincker and Wilbek, 1974). Coeliac disease may also predispose patients to malignant lymphoma (Holmes et al, 1976, Brandt et al, 1978).

Patients suffering from non-malignant immunoproliferative disorders like immunoblastic lymphadenopathy (Frizzera et al, 1974) and the acquired immunodeficiency syndrome have an excess risk of developing malignant lymphoma (Ziegler et al, 1982, Snider et al, 1983).

An immunodeficiency in HD at diagnosis is clinically characterized by skin anergy and in blood tests by a T-cell hypofunction (Kaplan, 1980). Defects in T-cell mitogen activation of blood lymphocytes have been found in other, apparently healthy family members to immunodeficient HD patients (Björkholm et al, 1978) and in healthy twin siblings to patients with Hodgkin's disease (Björkholm et al, 1977).

Familial factors

Relatives of patients with HD experience an increased risk of HD (Razis et al, 1959, Grufferman et al, 1977, Kerzin-Storarr et al, 1983). An elevated incidence of hematological malignancies has been observed among first degree relatives of females with NHL (Olsson and Kristoffersson, 1983). However, the overall risk of malignant disease among first degree relatives of patients with NHL may be low compared to the risk among family members of e.g. breast cancer cases (Olsson and Kristoffersson, 1983). Multiple cases of NHL have been described among close relatives (Greene, 1982).

Exposure to ionizing irradiation

Among survivors of the atomic bombs in Japan, an excess of malignant lymphoma has been reported (Nishiyama et al, 1973, Beebe et al, 1978). Patients irradiated for ankylosing spondylitis are also at increased risk of malignant lymphoma (Court-Brown and Doll, 1965). We have also found that, compared to controls, patients with malignant lymphoma have been treated more often with ionizing irradiation for benign disorders. Lymphomas following irradiation for benign disorders are seemingly often initially located near the site of irradiation (Olsson and Brandt, unpublished results).

Infectious agents

There is a possible causal link between development of Burkitt's lymphoma and Epstein-Barr (EB) virus infections (Morrow, 1982). Malaria infection has also been given an important role in the causal chain of events prior to the diagnosis of Burkitt's lymphoma (Morrow, 1982). Burkitt's type of lymphoma in non-endemic areas is to a much smaller extent associated with EB-virus infections (Morrow, 1982).

In the search for the etiology of the acquired immunodeficiency syndrome (AIDS), virus infections have been considered possible causal factors (Francis et al, 1983), e.g. cytomegalovirus and human T-cell leukemia virus (HTLV) (Francis et al, 1983). In the Caribbean Islands and in southern Japan, lymphomas may be caused by HTLV. This type of lymphoma is associated with skin infiltrates, osteolytic bone destructions and hypercalcemia (Essex, 1982). The lymphoma cells are of T-cell origin (Essex, 1982). In our region this virus is obviously not an important risk factor for malignant lymphoma. Thus none of 130 consecutive sera from lymphoma patients had antibodies to this virus (Blomberg et al, 1984). Similar results have been obtained in other parts of northern Europe (Dölken et al, 1983). Other retroviruses may be etiological factors in malignant lymphoma and much research is at present being pursued in this field (Barré-Sinoussi et al, 1983).

In Hodgkin's disease it has been found that patients prior to diagnosis more often than controls have had infectious mononucleosis (Miller and Beebe, 1973, Conelly and Christine, 1974, Rosdahl et al, 1974, Muñoz et al, 1978, Kvale et al, 1979). Since mononucleosis is caused by EB-virus, it may be that for some cases of HD EB-virus is a causal factor.

Drugs

The anticonvulsant agent phenytoin may cause lymphadenopathy, which resolves when the drug is discontinued (Gams et al, 1968). It has been reported, however, that some cases may progress to malignant lymphoma (Harrington et al, 1962). Dapsone, used in the treatment of leprosy and malaria, has given an excess of lymphoma when administered to laboratory animals (NCI, 1977). Amphetamine usage has also been associated with risk of HD (Newell et al, 1973, Henderson et al, 1979). Combination chemotherapy together with radiotherapy in HD may cause NHL (Krikorian et al, 1979).

Occupation

Chemists have been found to be at an increased risk of developing HD and NHL (Li et al, 1969, Olin, 1976, Olin and Ahlbom, 1980, Searle, 1978). It has been demonstrated that occupations indicating benzene exposure are associated with an increased risk of HD and NHL (Vianna and Polan, 1979). However, this was not confirmed in another study (Smith and Norelle Lickiss, 1980). Rubber factory workers may also have an excessive risk of developing malignant lymphoma (Monson and Nakano, 1976, Monson and Fine, 1978, McMichael et al, 1976). Anaesthesiologists (Vessey, 1978), veterinarians (Blair, 1980, Blair, 1982), vinyl chloride workers (Chiazze et al, 1977), workers at refineries (Tabershaw and Cooper, 1974, Thomas et al, 1982), processors of ore containing arsenic (Axelson et al, 1978) may be at risk of contracting lymphoma. In HD there is also a consistent association between woodwork and development of malignant lymphoma (Hodgkin, 1832, Milham, 1967, Milham and Hesser, 1967, Petersen and Milham, 1974, Grufferman et al, 1976, Greene et al, 1978, Abramson et al, 1978).

Proposed clusters of cases of HD in schools (Vianna et al, 1971) and an increased risk of HD among teachers (Vianna and Polan, 1973, Milham, 1974) have not been confirmed in more recent studies (Hoover, 1974, Grufferman et al, 1976).

Exposure to phenoxyacetic acids (Hardell et al, 1981), chlorophenols (Hardell et al, 1981), and exposure to electric fields (Greene, 1982, Wertheimer and Leper, 1979) have been proposed to induce malignant lymphoma. Exposure to asbestos has been suggested as a risk factor of malignant lymphoma (Ross et al, 1983), although two Swedish studies have not confirmed these results (Bengtsson et al, 1982, Olsson and Brandt, 1983). A possible association between exposure to herbicides and related

chemicals and an increased risk of malignant lymphoma of the skin has been suggested (Olsson and Brandt, 1981, Bishop and Jones, 1981). Exposure to organic solvents has been found to be a risk factor for malignant lymphoma in northern Sweden (Hardell et al, 1981).

The rationale for studying exposure to organic solvents as a lymphoma risk factor

Already in 1972 Aksoy noted that acute leukemia was unduly common in Turkish shoe workers exposed to benzene (Aksoy, 1972). Among these workers, several cases of HD were also observed (Aksoy, 1974). Later Capurro described a community where an excessive number of malignant lymphomas occurred. This community was characterized by factories emitting organic solvents as air pollution (Cappuro, 1979).

Among the risk occupations previously described (e.g. chemists, rubber workers, wood workers), occupational exposure to organic solvents occurs frequently and might be a common denominator for their occupational risk. Because organic solvents are volatile, the lymphoid tissue regional to the respiratory tract might be more extensively exposed than lymphoid tissue below the diaphragm. A rationale therefore exists for studying different sites of lymphoma presentation in relation to occupational exposure to organic solvents.

The rationale for studying sex hormones and reproductive factors in patients with malignant lymphoma

Results of some experimental studies suggest a relation between reproductive factors and the development of malignant lymphoma. In cats and dogs, the gonadal function is of importance for the risk of malignant lymphoma. An early neutering decreases the risk of lymphoreticular disease while a late neutering will increase the risk of malignant lymphoma (Schneider, 1983).

Lymphatic tumours are common if irradiated mice are treated with estrogen while myeloid tumours occur more often following testosterone treatment (Duplan, 1976).

New Zealand black (NZB) mice are prone to develop lymphoreticular malignancies and autoimmunity (Steinberg et al, 1979). If male NZB are castrated, the mortality due to such disorders is greatly enhanced. The

administration of testosterone abrogates this effect of orchiectomy (Roubinian et al, 1979).

Little is known about the relation between fertility and the risk or outcome of lymphoproliferative diseases in animals.

In some men with malignant lymphoma a gonadal injury may be present already prior to therapy manifested by a low sperm count and a low plasma testosterone concentration (Vigersky et al, 1982). A low S-FSH and a high P-prolactin level also suggested pituitary abnormalities in men with HD disease (Vigersky et al, 1982).

Some patients with immunodeficiency syndromes who carry a high risk of lymphoma may have an altered gonadal function, e.g. patients with ataxia teleangiectasia (Spector et al, 1978). An altered sexual function is present in another group of men with a high risk of developing malignant lymphoma, i.e. homosexual men with the acquired immunodeficiency syndrome (Metroka et al, 1983). Viral infections are suspected of being of etiologic importance in malignant lymphoma (Greene, 1981) and orchitis may follow infections with e.g. mumps and Coxsackie B viruses (Renard and Celers, 1970). Titers of cytomegalovirus are considerably higher in semen than in other secretions (Lang and Kummer, 1972).

To our knowledge the fertility prior to diagnosis in men with malignant lymphoma has not been studied. In women with HD a low parity preceding diagnosis has been suggested (Abramson et al, 1978).

AIMS OF THE PRESENT INVESTIGATION

The aims of the present investigation were to study:

1. Occupational risk factors associated with the development of malignant lymphoma with special emphasis on exposure to organic solvents.
2. Clinical variables such as tumour stage and site of tumour presentation in relation to occupational risk factors in non-Hodgkin's lymphoma.
3. Sex hormone levels in men with malignant lymphoma and their relation to risk factors.
4. Fertility in men and women prior to diagnosis of malignant lymphoma with special attention given to age of the father/mother, number of children, and the relation between these variables and occupational risk factors.

MATERIALS AND METHODS

Materials

Three case-referent studies in men with malignant lymphoma were performed to evaluate occupational exposure to chemicals and organic solvents. Two additional case-referent studies in male patients were performed to evaluate gonadal function and fertility prior to therapy in relation to the occupational history. In one case-referent study of women with malignant lymphoma, fertility prior to therapy was studied.

In Table I the cases and referents in each study are described.

Methods

Occupational histories (papers I, II, III, IV, V)

In paper I occupational information was derived from hospital records. In papers II-V the occupational information was obtained as follows. All patients and referents were interviewed using a standardized questionnaire. Occupations from school age up to the date of the interview were recorded. The period for each occupation and the name and address of the employer were registered. A description was obtained of the various tasks during an average work day in each occupational period. When handling of chemicals was spontaneously mentioned as a work task, the interviewee was asked to define the chemicals used. He was asked whether the handling of chemicals was sporadic or occurred every work day. If the composition of the chemicals used was unknown, the employer and/or the manufacturer was contacted by letter for more information. In papers IV and V information was also gathered regarding herbicide exposure and exposure to therapeutic irradiation.

Exposure criteria (papers II-V)

The criteria for exposure were as follows.

Organic solvents: Each person who for at least one year had handled organic solvents every work day and had been exposed to the solvent(s).

Herbicides: Each person who occupationally for at least one day had been exposed to phenoxy acids.

Therapeutic irradiation: Each person who had been exposed at least once to therapeutic irradiation either for a benign disorder or another malignancy.

Hormonal assays (paper IV)

In 57 consecutive untreated men with malignant lymphoma blood samples were drawn at 08 00 a.m. P-testosterone, S-LH and S-FSH were analysed at the Department of Clinical Chemistry, Malmö General Hospital, with radioimmunoassay technique (Thorell and Larsson, 1978). No patient was treated with corticosteroids or other drugs known to affect the gonadal function.

Semen analyses (paper IV)

In 33 patients and 114 referents semen was collected by masturbation after at least three days of sexual abstinence. Volume of ejaculate, sperm concentration (mill/ml) and percentage of motile, dead and normal sperm cells were recorded. The percentages of sperms with various morphologic abnormalities were assessed and the admixture of leukocytes estimated. In addition, motility in a capillary tube and penetration in hen's ovalbumen were determined. The semen analyses were performed prior to diagnostic procedures which could affect sperm function, e.g. operation with anaesthesia. No patient was treated with corticosteroids or other drugs known to affect the gonadal function. The semen analyses were made at the Fertility laboratory, Department of Forensic Medicine, Lund.

Morphological classification and staging procedures (papers I-VI)

In all patients representative tumour material was obtained through biopsy and classified according to Rappaport (Rappaport, 1966) or Rye (Rosenberg, 1966) by experienced pathologists with special interest in lymphoma pathology. Clinical staging according to the Ann Arbor system (Carbone et al, 1971) was based on physical examination, chest X-ray, lymphangiography, abdominal CT-scan and scintigraphy of the liver and spleen. In addition to biopsy from a representative lymph node or from extranodal lesions, fine-needle aspiration biopsies were obtained from lymph nodes with questionable abnormal size or structure visualized on lymphangiography or CT-scan and from liver and spleen. Bone marrow biopsies from the iliac crest were performed in all patients and peripheral blood smears were examined in all. Multiple biopsies from Waldeyer's ring were obtained in all patients. Diagnostic laparotomy were performed in the HD patients with tumour stage I-II but not in those with NHL. The presence or absence of B-symptoms was recorded in each patient.

According to the result of the staging procedures the patients with NHL (paper III) were divided into three categories: stage I-II lymphoma located above the diaphragm, stage I-II located below the diaphragm, and stage III-IV.

Fertility history (paper V and VI)

The fertility of patients and referents was recorded by interview. The age of the father/mother at the birth of each child was recorded. Early and late abortions were excluded but stillbirths were included. The interviewee was instructed to disregard adopted children.

Statistical methods (paper I-VI)

In table II the study design, the univariate and multivariate statistical methods are given. When the distribution of the values was skewed, either non-parametric tests were used or normality was induced by logarithmic transformation of the original values.

Table I. Definition of cases and referents for each study (each study is referred to by Roman numerals)

Study	Cases	Referents	Age restriction
I	Consecutive men with HD seen at the Department of Oncology, Lund, 1972-1978	1. Men with non-malignant diseases seen at the Department of Medicine, Lund, 1977 2. Men with allergy seen at the Department of Medicine, Lund, 1977 3. Consecutive men with chronic leukemias seen at the Department of Medicine, Lund, 1969-1977	20-65 yrs
II	Consecutive men with HD seen at the Department of Oncology, Lund, 1978-1979	1. Men in the general population matched with the patients for age and residence	20-65 yrs
III	Consecutive men with NHL seen at the Department of Oncology, Lund, 1978-1980	1. None. Internal comparison	None
IV (hormonal study) (sperm tests)	Consecutive men with HD and NHL seen at the Department of Oncology, Lund, 1979-1981 Consecutive men with HD and NHL seen at the Department of Oncology, Lund, 1979-1981, who were motivated and not severely ill	1. None. Internal comparison 1. Men undergoing sperm tests prior to vasectomy at the Department of Forensic Medicine, Lund, 1978-1980	None <65 yrs
V	Consecutive men with HD and NHL seen at the Department of Oncology, Lund, 1979-1980	1. None. Internal comparison 2. Consecutive men with bladder cancer seen at the Departments of Oncology and Urology, Lund, 1980-1983 3. Men with acute medical illness seen at the Department of Medicine, Lund, 1981	None ≥30 yrs

Consecutive women with HD and NHL
seen at the Department of Oncology,
Lund, 1980-1982

None

1. Consecutive men with thyreotoxicosis
seen at the Department of Oncology,
Lund, 1982
 2. Women with acute medical illness seen
at the Department of Medicine, Lund,
1981-1982
 3. Outpatient controls seen at Dalby
Community Health Research Center, Dalby,
1980
 4. Consecutive women with breast cancer
seen at the Department of Oncology, Lund,
during two periods 1980 and 1982
-

Table II. Statistical methods

Study	Study design	Analysis	
		Univariate	Multivariate
I	Case-control	Fisher's exact test	-
II	Case-control (matched)	Relative risk (Miettinen)	-
III	Case-control	Chi-square test	-
IV	Case-control	Analysis of variance	Regression analysis Discriminant analysis Analysis of covariance
V	Case-control	Chi-square test	Regression analysis Discriminant analysis Analysis of covariance Logistic regression analysis
VI	Case-control (matched)	Mantel-Haenszel Chi-square test	-
	Case-control	Analysis of variance	Regression analysis
		Chi-square test	Logistic regression analysis

RESULTS

Occupational risk factors with special emphasis on exposure to organic solvents (papers I and II)

By comparing occupational titles obtained from patient charts, the incidence of occupations indicating exposure to chemicals was studied (paper I). Chemists, painters and sprayers, glass and pottery workers, chemical processing workers, rubber product workers, plastic workers and photographic laboratory workers were occupations considered to indicate a high degree of chemical exposure. The cases comprised 88 consecutive men with HD seen at the Department of Oncology in Lund between 1973-1978. As referents, three different groups of men were used; one hundred consecutive men with non-malignant disorders treated at the Department of Medicine, Lund, 100 men seen at the Department of Allergology, Lund, and 32 men with chronic leukemia treated at the Department of Medicine. The study was restricted to men between 20 and 65 years of age.

The occupational titles suggested that about 20 % of the patients with HD had been occupationally exposed to chemicals. Among the referents about 2-3 % had similar occupations. The exposure rate in the referent groups was similar to the prevalence of such occupations in Sweden (2 %). Chemical occupations increased among the lymphoma cases with age suggesting that exposure to chemicals may be especially important as a risk factor for older patients.

In paper II a case-control study was performed comparing 25 consecutive men with HD and 50 referents from the general population matched for sex, age and parish. Using a standardized personal interview, occupational exposure to organic solvents was recorded. Each individual who for at least one year every work day within the last ten-year period had been exposed to organic solvents was considered exposed. The study was restricted to men between 20 and 65 years of age. Forty-eight per cent of the cases and 12 % of the referents were occupationally exposed to organic solvents ($p < 0.0005$, relative risk 6.6, 95 % CI 1.8-23.8). If the exposure time was extended further beyond the nearest ten-year period, 48 % of the cases and 16 % of the referents were still exposed. The median duration of exposure was 8 years and the median latency time was 10.5 years. In 9 out of the 12 exposed cases, exposure to aromatic organic solvents was found.

Occupational exposure to organic solvents and site of lymphoma presentation (paper III)

In 61 consecutive men with NHL seen at the Department of Oncology, Lund, the site of tumour presentation was investigated in relation to occupational exposure to organic solvents. After the initial staging the patients were divided into three categories: stage I-II above diaphragm, stage I-II below the diaphragm and stage III-IV. Occupational exposure to organic solvents for at least every work day during one year had occurred in 23 patients and 38 patients were non-exposed. Twelve out of fifteen patients (80 %) with stage I-II above the diaphragm were exposed to organic solvents while only one out of nine (11 %) of the patients with stage I-II below the diaphragm was exposed. In patients with stage III-IV ten out of thirty-seven (27 %) were exposed. There were significantly more exposed patients with stage I-II disease above the diaphragm ($p < 0.0003$). The exposed and non-exposed patients did not differ significantly in mean age at diagnosis or in histology according to the Rappaport classification.

Characterization of a subgroup of men with malignant lymphoma and an impaired testicular function at diagnosis (paper IV)

In 57 consecutive untreated men with HD and NHL the gonadal function was studied by measuring the hormones S-FSH, S-LH and P-testosterone. In 33 men with HD or NHL semen was analysed at diagnosis. The results of the hormonal and semen analyses were related to the presence or absence of prior occupational exposure to organic solvents. For the sperm tests 110 healthy, fertile men who had decided to undergo vasectomy served as referents.

Unexposed patients had significantly lower levels of P-testosterone compared to the exposed patients ($p < 0.002$). Controlling for age and clinical stage did not change the results. S-LH was higher among the unexposed patients after controlling for age ($p < 0.05$), while S-FSH did not significantly differ between unexposed and exposed patients.

With increasing age, S-FSH and S-LH became higher ($p < 0.001$ and $p < 0.001$ respectively), but P-testosterone remained unchanged. P-testosterone was lower in patients with more advanced tumour stage ($p < 0.02$), while S-FSH and S-LH were not related to tumour stage.

In a discriminant analysis comparing exposed and non-exposed lymphoma patients using P-testosterone, S-LH, S-FSH, tumour stage, HD/NHL and age,

P-testosterone was the best discriminator between the two groups ($p < 0.004$). S-LH also differed between the two groups ($p < 0.08$), but the effect was not significant after controlling for P-testosterone ($p > 0.4$).

The concentration of sperm cells was significantly lower among non-exposed patients than in exposed patients ($p < 0.0004$) and was also lower than in the reference group ($p < 0.001$). Controlling for age and tumour stage did not change the results. Sperm penetration in ovalbumen was significantly impaired among the non-exposed patients compared with the healthy reference group ($p < 0.001$). There was no significant difference between exposed patients and the reference group regarding sperm concentration and sperm penetration ($p > 0.1$).

Fertility prior to diagnosis in men with malignant lymphoma (paper V)

In 150 men with malignant lymphoma (51 HD and 99 NHL) fertility was studied prior to therapy by recording the number of their children and the year of birth for each child. Men, who every work day for at least one year had handled organic solvents, men who for at least one day had used herbicides occupationally, and men who had been treated with ionizing irradiation were considered exposed to risk factors of malignant lymphoma ($n=72$). In 78 other men with malignant lymphoma, such exposure was not evident.

Unexposed patients

In the unexposed group the proportion of childless men was significantly larger (40 %) than in the exposed group of lymphoma patients (18 %, $p < 0.001$). The number of childless men among the unexposed lymphoma patients was also larger than in a reference group of patients with bladder cancer (18 %, $p < 0.001$) and in another reference group of men with acute medical illness (20 %, $p < 0.03$).

The average number of children, 1.24, fathered by the unexposed patients was significantly lower than in the exposed patients, 2.13, ($p < 0.001$) and among the bladder cancer patients, 1.95, ($p < 0.004$).

The number of children was on the average 1.74 per patient in the group with acute medical illness. This number was, however, not significantly different from the unexposed lymphoma cases.

Exposed patients

Exposed lymphoma patients had significantly more children than men with acute medical illness ($p < 0.02$), but did not differ in fertility from the patients with bladder cancer.

The type of lymphoma (HD or NHL) did not influence the results. Among the patients who had fathered children the exposed group had significantly more children than the unexposed group ($p < 0.03$).

It could be shown in an age-matched analysis, between solvent-exposed patients and unexposed patients, that even prior to the start of the solvent-exposure fertility was higher in the solvent-exposed group and was not changed by the exposure.

The results of the fertility studies are summarized in Figs 1 and 2.

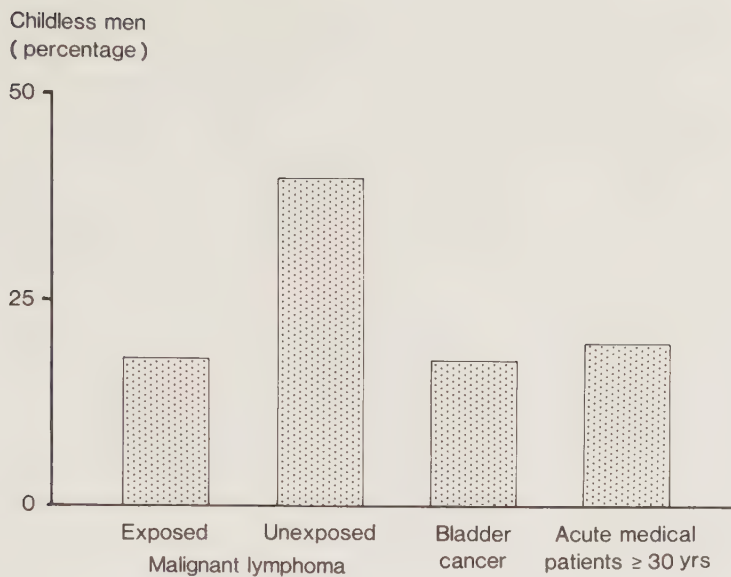


Fig 1.

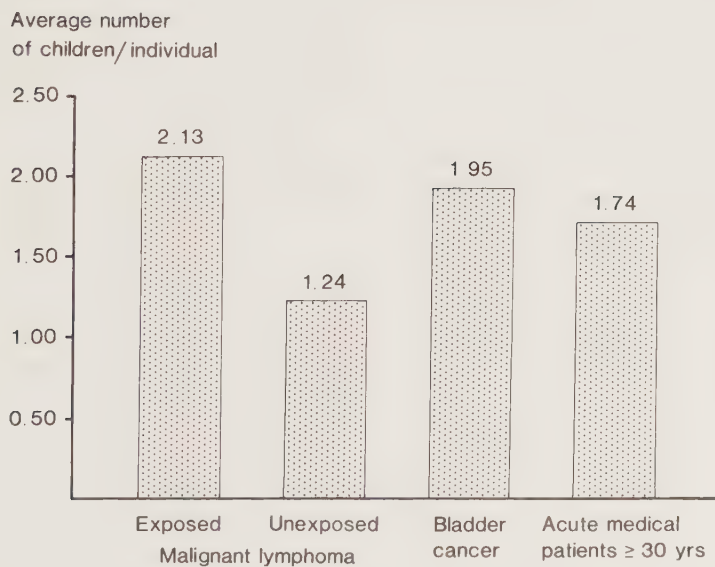


Fig 2.

Fertility in females with malignant lymphoma (paper VI)

The reproductive history was analysed in 117 women with malignant lymphoma (38 HD and 79 NHL) and compared to various reference groups of women (thyreotoxicosis, n=98, acute medical illness, n=172, and outpatient controls, n=188). The reference groups were combined because there was no significant difference in fertility between the groups. A comparison was also made between fertility in lymphoma patients and in a group of women with breast cancer (n=173).

A late age at first full term pregnancy (AFFP) was found to be a strong risk factor for women with NHL and possibly also for women with HD. The odds ratio for a woman to have her first child at 30 years of age was for NHL 7.2 (95 % CI 1.7-30.6) and for HD 4.8 (95 % CI 0.6-41.3) when compared to the three reference groups without malignant disorders. The odds ratio for women with breast cancer was lower 3.9 (95 % CI 1.2-12.8). Thus a late AFFP seems to be an even stronger risk factor for malignant lymphoma than for breast cancer.

If a late AFFP was combined with a low parity (1-2 children), the risk of lymphoma was further increased indicating that low parity might constitute a weak risk factor for malignant lymphoma.

There was no significant difference between the groups regarding the number of nulliparous women and the average number of children. Nor was there any significant difference between women with HD and NHL in regard to AFFP, number of children or childlessness.

DISCUSSION

General considerations

The incidence of malignant lymphoma is relatively low and in order to evaluate risk factors large cohorts of exposed and unexposed individuals would be required. For the present studies it was therefore considered more feasible to use case-referent methods.

In case-referent studies several types of bias must be considered (Kleinbaum et al, 1982).

Selection bias

Are the patients studied representative of lymphoma cases in general in our region? Approximately 80 % of the eligible men with HD in the region are examined at our clinic. The corresponding figure for men with NHL is 55 % and for the age group 20-70 years 70 %. Socio-economic bias in referral patterns is probably negligible because of the uniform health care system in the region. However, some old and severely ill patients are not referred. Since consecutive patients were studied, we feel that the material investigated is representative of malignant lymphoma in southern Sweden. For old and very sick lymphoma patients the data may, however, be less reliable.

Are the reference groups subjected to bias? As shown in Table I, two different sources of controls were used for comparison with the lymphoma patients: population based controls (paper II) and hospital based controls (papers I, IV, V, VI). Moreover, comparisons between groups of lymphoma patients were made in papers III, IV and V.

When hospital based controls were used the validity of the control material was strengthened by using more than one group of controls (papers I, V, VI) or by making a comparison between subgroups of lymphoma patients (papers IV and V).

The cases and referents were of similar age and in two of the studies (papers II and V) age-matched analyses were performed. In the statistical analyses, the possibility of age effects was checked. In three of the studies, age restrictions were employed (papers I, II and IV).

The geographical origin of cases and referents in the different studies needs some comment. In paper I the cases with HD came from the whole region, while the referents were living in the vicinity of our hospital. Thus, a geographical selection bias is possible although more than half of the HD patients also came from the immediate vicinity of Lund. In paper II, cases and referents were matched for residence (parish) and a geographical selection bias is unlikely. Neither is such a bias a problem in study III and IV. In paper V one of the referent groups, men with acute medical illness, was recruited from the immediate vicinity of our hospital and might introduce a bias. However, another reference group, men with bladder cancer, was admitted from the whole region, and the use of an internal comparison among the lymphoma cases was not likely to introduce a selection bias. In paper VI referents both from the whole region (women with thyreotoxicosis) and from the vicinity of Lund (women with acute medical illness and out-patient controls) were used. Because comparable results were obtained using different reference groups, the geographical origin of the referents was not considered to bias the results.

A bias of socio-economic factors is not apparent except for study IV where men who wanted vasectomy were used as referents. This group might be especially fertile. However, no other healthy reference group was available. The conclusion that low sperm concentration is characteristic of unexposed patients is therefore mainly based on the comparison between unexposed and exposed men with lymphoma. According to a recent analysis, the distribution of social classes is not significantly different among unexposed and exposed patients with malignant lymphoma (Olsson and Brandt, unpublished results).

Information bias

Is the recall of exposure different in cases and referents? For several reasons a selective recall of exposure was not considered to be a serious bias in the present studies. Firstly, the heavy exposure criterion for solvents involving a daily exposure for at least one year reduced the risk of a recall bias. Secondly, the results in papers II-IV are based on comparisons between subgroups of lymphoma patients and it is difficult to perceive that the recall is different in subsets of patients with the same disease. Thirdly, cases or referents rarely refused to participate in the studies, thereby reducing the risk of a potential bias.

Is there a possibility of an interviewer's bias? The interviewer knew

whether the interviewee was a case or a referent and this might constitute a potential bias. Because of the study design and the interview questionnaire used, it was not regarded feasible to perform the interviews blind. The highly structured interview and the use of a "heavy exposure criterion" probably reduced the risk of observer's bias. Moreover, the interviews with the lymphoma patients were performed prior to the staging of the tumour and prior to the hormonal and sperm tests thus reducing the possibility of an observer's bias.

We have no reason to believe that any serious bias affected the recording of the fertility variables in the cases and referents.

Problems of possible confounding, the validity of studied variables and the coherence of the findings will be discussed below for each paper.

Papers I-III

Occupational exposure to chemicals was found to be more common among patients with HD than in various reference materials. This finding is in agreement with studies showing an increased risk of lymphoma among chemists (Li et al, 1969, Olin, 1976, Olin and Ahlbom, 1980, Searle, 1978). However, in some studies no relation between exposure to chemicals and malignant lymphoma has been observed (Benn et al, 1979, Fonte et al, 1982). One possible reason for discrepancies between various studies is that different methods of assessing exposure have been used (Grufferman, 1982). A bias may be introduced when occupational information is obtained from hospital records only (Fonte et al, 1982) if the quality of this information is poor. At our clinic a highly standardized history, including occupational history, is taken from all patients. Using patients with other malignant tumours as referents (Benn et al, 1979) may also constitute a bias.

Occupational exposure to chemicals was uncommon in patients 20-30 years of age, whereas in older patients exposure was more common. HD has a bimodal incidence and this has already been suggested to reflect different etiologies for different age groups (Mac Mahon, 1966). Thus, our results indicate that occupational exposure to chemicals may be important as a risk factor for older HD patients whereas other risk factors may be more important among younger patients.

In men occupationally exposed to organic solvents the relative risk of HD

was 6.6. This finding is in agreement with studies linking the development of HD and NHL (Hardell et al, 1981) and acute leukemia (Flodin et al, 1981) to prior exposure to solvents. The relative risk found by Hardell et al was 3.1 for lymphoma patients with a high degree of solvent exposure. For patients with acute leukemia the relative risk was 6.3 (Flodin et al, 1981). In the latter study, an effect modification because of background irradiation was found in the patients exposed to solvents. Results of chromosome studies of bone marrow cells are also in line with a relation between occupational exposure to solvents and the development of acute leukemia. Thus clonal chromosome aberrations at diagnosis are more common among exposed patients than in patients without any history of exposure. Moreover, there is a prevalence of certain chromosome abnormalities among the exposed patients (Mitelman et al, 1978, Mitelman et al, 1981).

There are several problems when recording exposure to organic solvents. Solvents are widely used at work and at home and presumably all adults have been exposed to some extent. To evaluate the possible risk of exposure to organic solvents it was considered important to study individuals with an extraordinarily high degree of exposure. In the present study, exposure was therefore defined as a daily handling of organic solvents for at least one year. Occupational handling of organic solvents generally means exposure to more than one solvent. Exposure to other chemicals dissolved in the solvent or chemicals used together with the solvent may also occur. Some products are coded by the manufacturer and it may be difficult to reveal their content. It may also be that some products formed when the chemical is manufactured or used are unknown to the manufacturer. In an attempt to overcome these difficulties supplementary information about the workplace and exposure was obtained from the manufacturer, employer, industrial safety inspector, or the company physician at the workplace. In some studies, an age restriction was employed (20-65 years of age, papers I and II) because occupational exposure rarely starts before 20 years of age and because recalling working conditions may be difficult for retired individuals. Despite attempts to define the solvents used by our patients it was not possible to discern whether the risk of malignant lymphoma is related to all kinds of organic solvents or whether the risk is due to exposure to a few solvents.

There is ample evidence that exposure to benzene may cause acute leukemia (IARC monograph, 1982). Embryotoxicity and genotoxicity have also been

noted (IARC monograph, 1982, Forni et al, 1971). Benzene is toxic to hematologic stem cells and may therefore be a risk factor also for malignant lymphoma (IARC monograph, 1982). Benzene may be present as an impurity in other products (IARC monograph, 1982) and it might be argued that the association between exposure to organic solvents and development of malignant lymphoma is due to benzene exposure. However, benzene has been classified as a poison in Sweden since 1972 and efforts have been made to reduce its presence as an impurity in solvents and petrochemical products. It is therefore unlikely that exposure to benzene was a major risk factor for patients with lymphoma.

Toluene and xylene were the most common solvents used by the lymphoma patients. It is not known whether these solvents may be tumourigenic in man. Exposure to toluene has been reported to cause chromosome changes in blood lymphocytes (Funes-Cravioto et al, 1977), but the evidence for this is not consistent (Mäki-Paakanen, 1980). Embryotoxic effects have not been established for toluene (Arbete och hälsa, 1981a). Little is known about possible mutagenic or teratogenic effects of xylene (Arbete och hälsa, 1981b). Developmental abnormalities in animals are suspected to occur at low levels of xylene exposure (Arbete och hälsa, 1981b). Styrene exposure had occurred in some lymphoma patients. Exposure to styrene has been associated with embryotoxic and genotoxic effects (Arbete och hälsa, 1981c, Högstedt, 1983).

In man little is known about possible genotoxic and embryotoxic effects of a mixed exposure to organic solvents. Beside direct mutagenic effects of organic solvents other possible mechanisms might be involved in the tumourigenesis. Solvents are lipidophilic (Carlsson and Ljungkvist, 1982) and are concentrated in fat tissue and cell structures rich in lipids. Such agents might cause membrane effects making carcinogens more easily penetrate the cell. They might also change antigenic structures and cause immunological effects predisposing to lymphoma.

The median latency time from the start of solvent exposure to diagnosis of lymphoma was 10.5 years (paper II) supporting other findings that lymphohaematopoietic tumours develop in a shorter time than other tumours (Boice and Land, 1982). Leukemia and lymphoma patients may be especially suitable for studies of environmental risk factors because relevant exposures may have occurred not long before the onset of disease.

When the tumour presentation at diagnosis was studied in patients with NHL in relation to solvent exposure, the patients were divided into stage I-II with initial manifestation above the diaphragm, I-II with initial manifestation below the diaphragm and stage III-IV with involvement on both sides of the diaphragm. In large clinical series about twenty per cent of the patients with NHL present with stage I-II disease (De Vita and Hellman, 1982). There is usually an understaging of the initial disease (De Vita and Hellman, 1982). It is, however, reasonable to assume that the initial lymphoma manifestation may represent the primary site of the disease. To study patients with local and disseminated disease may therefore be of relevance for the etiology even if understaging does occur. In our series of men with NHL 39 % had stage I-II indicating some understaging of the patients.

In Table III an enlarged series of 167 consecutive men with NHL is shown in relation to solvent exposure and initial tumour presentation (Olsson and Brandt, unpublished results). There is a highly significant relation between solvent exposure and supradiaphragmatic tumour presentation ($p < 0.001$). In the table, extranodal localized disease is regarded as stage I-II presentation, explaining the higher percentage of stage I-II disease compared with the original data presented in paper III.

In another investigation we have found that skin presentation of NHL is significantly related to herbicide exposure (Olsson and Brandt, 1981) and data from patients with possibly radiation induced NHL indicate an association between the site of tumour presentation and previous target volume for irradiation (Olsson and Brandt, unpublished results). Therefore the site of tumour presentation may be an important epidemiological variable in relation to the exposure site of responsible etiological agents.

Whether a different histology of the tumours (NHL) may be related to solvent exposure has not been assessed definitely. Our data from the crude division of NHL into histiocytic, mixed and lymphocytic lymphoma do not suggest such a relation. However, further studies will be performed employing the Kiel-classification (Lennert et al, 1978).

Table III. Extended material of patients with NHL describing initial tumour presentation in solvent exposed and nonexposed patients

	Stage I-II above diaphragm	Stage I-II below diaphragm	Stage III-IV
Exposed	32	13	19
Nonexposed	27	28	57

Papers IV-VI

Another major finding of this thesis is that men for whom no apparent risk factors can be discerned through a medical and occupational history have signs of an impaired gonadal function, i.e. relatively low levels of P-testosterone, high S-LH, low sperm concentration, subnormal sperm penetration in hen's ovalbumen and a low fertility (see Fig 3).

The impaired gonadal function prior to therapy was found both in HD and NHL. Although subnormal testicular function prior to therapy has previously been described in HD (Vigersky et al, 1982), the present results add the information that the gonadal function may also be impaired in untreated men with NHL. When investigating fertility in men, one might rather expect to find a low fertility following exposure to potential genotoxic agents, e.g. solvents, herbicides and irradiation. Instead, the reduced fertility was found in the group of lymphoma patients for whom no risk factors were documented. Because the impaired gonadal function was independent of tumour stage and presence of B-symptoms, it must be postulated that a reduced testicular function precedes the development of the malignant disease. Some unidentified etiologic agent(s) may be responsible for the impaired gonadal function and for the later occurrence of lymphoma in these men. However, it is also possible that an impaired gonadal function may pre-dispose for lymphoma development and that the reduced gonadal function is caused by e.g. genetic factors. Studies of healthy siblings and children of the patients might help to resolve these questions.

Since we have demonstrated a relationship between the site of presentation of localized lymphomas and the site of previous exposure to tumourigenic agents, we think that the genotoxic effect may be restricted to certain exposed regions of the body. More distant effects like a gonadal injury

are then less likely to occur. Exposure to other agents, e.g. virus infections might affect several organs including the gonads. Virus infections have been postulated to be risk factors for malignant lymphoma and exposure to virus may also be related to the gonadal insufficiency observed in a subgroup of lymphoma patients. Virus infections, for example, may cause orchitis (Renard and Celers, 1970) and in other instances virus may be present and concentrated in semen (Lang and Kummer, 1972).

Whether the hypothalamus/hypophysis and gonads are affected by solvent exposure is at present under study. Data for humans are scarce, although in animals effects on hypothalamus/hypophysis have been noted (Andersson et al, 1980). Our investigation indicated that fertility may be normal in men exposed to solvents.

While the sperm tests were performed in a selected group of men with lymphoma i.e. young, motivated, not severely ill individuals, the hormonal tests and the fertility histories were not subjected to selection bias. However, the results of all these modes of studying reproductive function, i.e. hormonal assays, sperm tests and assessment of fertility pointed in the same direction; a subgroup of men with malignant lymphoma displays a gonadal insufficiency.

For practical reasons, it was not possible to obtain more than one semen sample per patient prior to therapy. The validity of a single P-testosterone value has been found to be quite reliable in an epidemiological study (Dai et al, 1981). All blood samples in our study were drawn at 08 00 a.m. to reduce the possibility that circadian variations of the hormones might introduce a bias. The assay of P-testosterone may crossreact with dihydro-testosterone. S-LH crossreacts with HCG and to a smaller extent with S-TSH. Ectopic HCG production has not been described in malignant lymphoma and there were no signs of hypothyroidism among the patients. Thus, cross-reactivity with other hormones was in all probability not a bias in our investigation.

The determination of sperm concentration in occupational studies has been found to be more useful than the assay of the total number of sperms ejaculated (Whorton, 1984). Of the semen parameters studied, the difference between the exposed and unexposed patients was greatest regarding the sperm concentration, underlining the usefulness of this parameter as an

important variable in epidemiological investigations.

The finding of an impaired sperm penetration in hen's ovalbumen in unexposed lymphoma patients is interesting. The most common reason for a low sperm penetration is the presence of sperm autoantibodies on the sperm cells (Jagar et al, 1979). Autoimmune disorders are linked to a later development of malignant lymphoma (Louie and Schwartz, 1978, Brincker and Wilbek, 1974) and the finding of a low sperm penetration has prompted further investigations of autoimmune manifestations among the unexposed lymphoma patients. Autoimmune disorders, e.g. SLE, are more common in women than in men (Dubois, 1974) and this has been related to sex hormones (Inman, 1978). Testosterone treatment reduces the manifestations of autoimmunity in animals (Roubinian et al, 1979).

Following reports that child sex ratio may be altered in the offspring of individuals who have recently had virus infections or have autoimmune disorders (Alperovitch and Feingold, 1981, Drew et al, 1978, Langaney and Pison, 1979), we have previously studied child sex ratio prior to therapy in the offspring of patients with lymphoma. We found that in young men and women with NHL there was a predominance of females in the offspring (Olsson and Brandt, 1982). The reason for the altered child sex ratio is under further investigation.

There are some indications that hormonal factors may be of importance for the development of lymphoproliferative tumours. Radiation-induced leukemia in mice is more often lymphatic if the animals have been given estrogen treatment (Duplan, 1976), while myeloid leukemias are promoted by androgen treatment (Duplan, 1976). Age at neutering is of importance for the risk among cats and dogs of developing lymphoproliferative disease (Schneider, 1983). If the animals are neutered at birth their risk of developing tumours is reduced while neutering in adult life will increase the risk of lymphatic tumours (Schneider, 1983). If this animal model applies to humans, the gonadal insufficiency of men with malignant lymphoma may have been induced in adult life and prior to the development of the malignancy.

In humans, malignant lymphomas are unduly common in homosexual men with the acquired immunodeficiency syndrome (Metroka et al, 1983). In some homosexual men P-testosterone levels may be low (Kolodny et al, 1971, Kolodny et al, 1972). Studies of sex hormones in men developing lymphoma in this

setting would be of great interest.

There is also other evidence that hormonal factors may affect the risk of lymphoma. Ataxia teleangiectasia is a hereditary disease that predisposes to malignant lymphoma (Mc Farlin et al, 1972). Among other developmental defects these patients display a gonadal insufficiency (Mc Farlin et al, 1972). Klinefelter's syndrome has been associated with malignant lymphoma (Mac Sween, 1965) and with breast cancer (Vorherr, 1980). An estrogen excess may be present in these patients (Bardin and Paulsen, 1981).

To test further the hypothesis that reproductive factors might be of importance for the risk of malignant lymphoma a study of fertility was performed in women with malignant lymphoma (paper VI). Because women have a cyclic hormonal function which is also subjected to changes during puberty and menopause, we decided to study fertility variables rather than hormonal variables. A previous study has indicated that women with HD often have a low parity (Abramson, 1978). In that study, information about age at first full term pregnancy (AFFP) was not at hand.

We found that a late AFFP was a strong risk factor for malignant lymphoma and even stronger than the risk for breast cancer. A low parity increased this risk. This finding raises the possibility that hormonal factors in women may be of importance for lymphoma. A late AFFP would subject a woman to more menstrual cycles and to more peaks of the female sex hormones, e.g. estradiol.

Swedish women belonging to the highest or lowest social classes have a higher fertility than middle-class women (Bernhard, 1971). Although family size may be a social class indicator, recent studies of HD in England and Sweden have not demonstrated any clear-cut relationship between HD and social class (Registrar General, 1971, Registrar General, 1978, Hardell and Bengtsson, 1983).

The risk of HD has previously been found to increase with a reduction of sibship size (Gutensohn and Cole, 1977). The elevated risk of HD in small families may therefore be related to a low reproductive capacity rather than to socio-economic factors.

Impaired gonadal function in unexposed men with
malignant lymphoma

P-testosterone low

S-LH high

Oligo-/a-spermi

Low sperm penetration test in hen's ovalbumen

High percentage of childless men

Low average number of children

Fig 3. Hormonal and reproductive characteristics
in unexposed men with malignant lymphoma

CONCLUDING REMARKS

The findings presented in this thesis suggest that;

1. Occupations associated with extensive chemical exposure are common among patients with Hodgkin's disease. Such occupations are more common in older than in younger patients.
2. Occupational exposure to organic solvents is a risk factor for Hodgkin's disease. The risk of solvent exposure is associated with a relatively short latency period (median 10.5 years).
3. A history of occupational exposure to organic solvents is associated with a supra-diaphragmatic site of tumour presentation in non-Hodgkin's lymphoma.
4. A group of men with malignant lymphoma (Hodgkin's disease or non-Hodgkin's lymphoma), for whom there is no history of occupational exposure to organic solvents, is characterized by an impaired gonadal function at diagnosis. A low level of P-testosterone, a low sperm count and a subnormal sperm penetration in hen's ovalbumen are characteristic findings in this group of men.
5. Men with malignant lymphoma, without any occupational history of exposure to organic solvents, herbicides and who have never been treated with ionizing irradiation, have a reduced fertility compared to other lymphoma patients. Fertility in the unexposed group is also lower than in a group of men with bladder cancer and in another reference group of men with acute medical illness.
6. Women with malignant lymphoma, Hodgkin's disease and non-Hodgkin's lymphoma, have a later age at first full term pregnancy (AFFP) than controls. The risk associated with a low AFFP is even higher for lymphoma patients than for breast cancer patients. A low parity seems to augment the risk associated with a late AFFP.

The findings allow the formulation of the following hypotheses for future studies:

A group of men with HD or NHL is characterized by an extensive occupational exposure to chemicals, especially to organic solvents. In patients with NHL, the initial lesions occur mainly supradiaphragmatically close to the respiratory tract. Another large group of men with malignant lymphoma for whom no apparent occupational risk factors are present is characterized by an impaired gonadal function and a low fertility. The impaired testicular function might be caused by some still unidentified etiologic agent(s). Alternatively, a reduced gonadal function, hereditary or acquired, may predispose these men for malignant lymphoma.

Reproductive factors may be of importance for the development of lymphoma also in women, because a late age at first full term pregnancy was found to be a strong risk factor. Since the risk increases with a low parity, uninterrupted cyclic ovarian activity may be of importance.

Important issues to be investigated in the future are;

Does the occupational risk apply to all types of organic solvents?

Is the increased risk associated with exposure to organic solvents due to a direct genotoxic effect of the solvents?

Is the effect indirect, e.g. through facilitating the penetration of carcinogens through cell membranes?

Do chemical risk factors interact with other risk factors e.g. viral infections?

Do chemical risk factors cause changes in the immunological system promoting the development of malignant lymphoma?

What are the causes of the gonadal insufficiency in men and the altered reproductive age in females developing lymphoma?

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to

Associate Professor Lars Brandt, my tutor, who patiently has guided me in my scientific work. His great knowledge in haematology and in the epidemiology of lymphoproliferative disorders has been invaluable for my own research work.

Professor Dick Killander, head of the Department of Oncology, who introduced me into the field of oncology and through his great scientific interest has given me much encouragement and valuable criticism.

Associate Professor Torgil Möller, head of the Southern Swedish Regional Tumour Registry, for many helpful discussions connected with problems in cancer epidemiology.

Mr Bo Gullberg, B Sc, and Mr Jonas Ranstam, B Sc for statistical analyses and epidemiological advice.

Ms Gertrud Andersson for expert secretarial assistance of the final manuscript.

Mrs Birgitta Engdahl, Mrs Eva Henriksson and Mrs Mona Martinsson for skilful technical assistance.

Mr Claes Westrup, who by his great skill in computing made it possible for my data sheets to communicate with the statisticians.

Mrs Muriel Spalding for revising the English text.

The late Dr Paul E. Walker, I.A.C.S., Williamson, W.Va, U.S., who opened my interest in and made me choose the medical profession.

My parents and family for support and encouragement.

I also like to thank the nursing staff and my colleagues at the Department of Oncology for their assistance and support during the epidemiological studies.

Finally I like to thank all patients who despite a difficult time with illness took part in the investigations.

REFERENCES

- Abramson JH, Pridan H, Sacks MI, et al. A case-control study of Hodgkin's disease in Israel. *JNCI* 1978; 61: 307-314.
- Aksoy M, Dincol K, Erdem S, et al. Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. *Br J Ind Med* 1972; 29: 56-64.
- Aksoy M, Erdem S, Dincol K, et al. Chronic exposure to benzene as a possible contributory etiologic factor in Hodgkin's disease. *Blut* 1974; 28: 293-298.
- Alperovitch A, Feingold N. Sex ratio in offspring to patients with multiple sclerosis. *N Eng J Med* 1981; 305: 1157.
- Anderson JL, Bieber CP, Fowles RE, et al. Idiopathic cardiomyopathy, age and suppressor-cell dysfunction as risk determinants of lymphoma after cardiac transplantation. *Lancet* 1978; 2: 1174-1177.
- Andersson K, Fuxe K, Toftgård R, et al. Toluene-induced activation of certain hypothalamic and median eminence catecholamine nerve terminal systems of the nude rat and its effect on anterior pituitary hormone secretion. *Toxicology Letters* 1980; 5: 393-398.
- Arbete och hälsa. Scientific basis for Swedish occupational standards. Criteria group for occupational standards. National Board of Occupational Safety and Health, S-171 84 Solna, Sweden, 1981a; 21: 40-45.
- Arbete och hälsa. Scientific basis for Swedish occupational standards. Criteria group for occupational standards. National Board of Occupational Safety and Health, S-171 84 Solna, Sweden, 1981b; 21: 46-51.
- Arbete och hälsa. Scientific basis for Swedish occupational standards. Criteria group for occupational standards. National Board of Occupational Safety and Health, S-171 84 Solna, Sweden, 1981c; 21: 30-33.
- Axelsson O, Dahlgren E, Jansson C-D, et al. Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. *Br J Ind Med* 1978; 35: 8-15.

Bardin CW, Paulsen CA. The testes. In Textbook of Endocrinology, sixth edition (Editor Williams RH). W B Saunders Company, Philadelphia 1981; 318-322.

Barré-Sinoussi F, Cherman JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immunodeficiency syndrome (AIDS). Science 1983; 220: 868-870.

Beebe GW, Kato H, Land C. Studies of the mortality of A-bomb survivors. 6. Mortality and radiation dose, 1950-1974. Radiat Res 1978; 75: 138-201.

Bengtsson N-O, Hardell L, Eriksson M. Asbestos exposure and malignant lymphoma. The Lancet 1982; ii: 1463.

Benn RT, Mangood A, Smith A. Hodgkin's disease and occupational exposure to chemicals. Br Med J 1979; 2: 1143.

Bernhard E. Trends and variation in Swedish fertility - A cohort study. Urval, Statistiska Centralbyrån, Stockholm, 1971; 5.

Bishop CM, Jones AH. Non-Hodgkin's lymphoma of the scalp in workers exposed to dioxins. Lancet 1981; ii: 369.

Björkholm M, Holm G, de Faire U, et al. Immunological defects in healthy twin siblings to patients with Hodgkin's disease. Scand J Haematol 1977; 19: 396-404.

Björkholm M, Holm G, Mellstedt H. Immunological family studies in Hodgkin's disease. Is the immunodeficiency horizontally transmitted? Scand J Haematol 1978; 20: 297-305.

Blair A, Hayes HM Jr. Causes of death among US veterinarians, 1966-1977. Int J Cancer 1980; 25: 181-185.

Blair A, Hayes HM Jr. Mortality patterns among US veterinarians, 1947-1977. An expanded study. Int J Epidemiology 1982; 11: 391-397.

Blomberg J, Nilsson I, Kjellen L, et al. Antibodies to HTLV I associated antigens in Scandinavian patients and blood donors (submitted for publication).

Boice JD, Land CE. Ionizing radiation. In Cancer Epidemiology and Preven-

tion (Editor Schottenfeld D, Fraumeni JF). W B Saunders company, Philadelphia 1982; 231-253.

Brandt L, Hagander B, Norden Å, et al. Lymphoma of the small intestine in adult coeliac disease. *Acta Med Scand* 1978; 204: 467-470.

Brincker H, Wilbek E. The incidence of malignant tumours in patients with respiratory sarcoidosis. *Br J Cancer* 1974; 29: 247-251.

Cancer incidence in Sweden 1978. The National Board of Health and Welfare. The cancer registry.

Cancer incidence in Sweden 1979. The National Board of Health and Welfare. The cancer registry.

Cancer incidence in Sweden 1980. The National Board of Health and Welfare. The cancer registry.

Cantor KP, Fraumeni JF Jr. Geographic and temporal patterns of non-Hodgkin's lymphoma. Mortality in U.S. counties, 1950-1975. *Cancer Res* 1980; 40: 2645-2652.

Cappuro PU. Cancer in a community subject to air pollution by solvent vapors. *Clin Toxicol* 1979; 14: 285.

Carbone PP, Kaplan HS, Musshof K, et al. Report of the committee on Hodgkin's disease staging. *Cancer Res* 1971; 31: 1860-1861.

Carlsson A, Ljungkvist E. Exposure to toluene. Concentration in subcutaneous adipose tissue. *Scand J Work Environ Health* 1982; 8: 56-62.

Chiazze L Jr, Nichols WE, Wong O. Mortality among employees of PVC fabricators. *JOM* 1977; 19: 623-628.

Cohen BM, Smetana HF, Miller RW. Hodgkin's disease: long survival in a study of 388 world war II army cases. *Cancer* 1964; 17: 856-866.

Cole P, MacMahon B, Aisenberg A. Mortality from Hodgkin's disease in the U.S. *Lancet* 1968; ii: 1371-1376.

Connelly RR, Christine BW. A cohort study following infectious mononucleosis. *Cancer Res* 1974; 34: 1172-1178.

Correa P, O'Connor GT. Epidemiological pattern of Hodgkin's disease. *Int J Cancer* 1971; 8: 192-201.

Court-Brown WM, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965; 2: 1327-1332.

Dai WS, Kuller LH, LaPorte RE, et al. The epidemiology of plasma testosterone levels in middle-aged men. *Am J Epidemiol* 1981; 114: 804-816.

De Vita Jr VT, Hellman S. Hodgkin's disease and non-Hodgkin's lymphomas. In *Cancer. Principles and practice of oncology*. (Editors De Vita Jr VT, Hellman S, Rosenberg SA). J B Lipincott company, Philadelphia 1982; 1331-1401.

Drew JS, London WT, Lustbader ED, et al. Hepatitis B virus and sex ratio of offspring. *Science* 1978; 201: 687-692.

Dubois EL. The clinical picture of systemic lupus erythematosus. *Lupus Erythematosus*. Second edition. (Editor Dubois EL). Los Angeles, University of Southern California Press 1974; 232-242.

Duplan JF. Neoplasms of hematopoietic systems. In *Scientific Foundations of Oncology*. (Editor Symington T, Carter RL). William Heinemann Medical Books Ltd, London, 1976; 444-456.

Dölken G, Bross KJ, Chosa T, et al. No evidence for HTLV infections among leukemia patients in Germany. *Lancet* 1983; ii: 1495.

Essex M. Adult T-cell leukemia-lymphoma: role of a human retrovirus. *J Natl Cancer Inst* 1982; 69: 981-985.

Flodin U, Andersson L, Anjou C-G, et al. A case-referent study on acute myeloid leukemia, background radiation and exposure to solvents and other agents. *Scand J Work Environ Health* 1981; 7: 169-178.

Fonte R, Grigis L, Grigis P, et al. Chemicals and Hodgkin's disease. *Lancet* 1982; ii: 50.

Forni A, Pacifico E, Limonta A. Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health* 1971; 22: 373-378.

Francis DP, Curran J, Essex M. Epidemic acquired immune deficiency syndrome: epidemiologic evidence for a transmissible agent. *JNCI* 1983; 71: No. 1, 1-4.

Fraumeni JF Jr, Hoover R. Immunosurveillance and cancer: epidemiological observations. *Natl Cancer Inst Monogr* 1977; 47: 121-126.

Frizzera G, Moran EM, Rappaport H. Angio-immunoblastic lymphadenopathy with dysproteinaemia. *Lancet* 1974; 1: 1070-1073.

Funes-Cravioto F, Kolmodin-Hedman B, Lindsten J, et al. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rototyping factory and in children of women laboratory workers. *Lancet* 1977; 2: 322-325.

Gams RA, Neal JA, Conrad FG. Hydantoin-induced pseudo-pseudolymphoma. *Ann Intern Med* 1968; 69: 557-568.

Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency diseases. *Cancer* 1971; 28: 89-98.

Greene MH, Brinton LA, Fraumeni JF Jr, et al. Familial and sporadic Hodgkin's disease associated with occupational wood exposure. *Lancet* 1978; ii: 626-627.

Greene MH. Clinical and environmental predisposing factors. pp 218-222 in (moderator Berard CW) *A multidisciplinary approach to non-Hodgkin's lymphomas*. *Ann Intern Med* 1981; 94: 218-235.

Greene MF. Non-Hodgkin's lymphoma and mycosis fungoides. In *Cancer Epidemiology and Prevention*. (Editors Schottenfeld D, Fraumeni JF). W B Saunders company, Philadelphia, 1982; 754-778.

Grufferman S, Duong T, Cole P. Occupation and Hodgkin's disease. *JNCI* 1976; 57: 1193-1195.

Grufferman S, Cole P, Smith PG, et al. Hodgkin's disease in siblings. *New Engl J Med* 1977; 296: 248-250.

Grufferman S. Hodgkin's disease. In Cancer Epidemiology and Prevention. (Editors Schottenfeld D, Fraumeni JF). W B Saunders company, Philadelphia, 1982; 739-753.

Guralnick L. Mortality by occupation (or industry) and cause of death among men 20-64 years of age. United States, 1950. Vital Statistics Special Report 1963; 53: 95-433.

Gutensohn N, Cole P. Epidemiology of Hodgkin's disease in the young. Int J Cancer 1977; 19: 595-694.

Hardell L, Bengtsson NO. Epidemiological study of socioeconomic factors and clinical findings in Hodgkin's disease, and reanalysis of previous data regarding chemical exposure. Br J Cancer 1983; 48: 217-225.

Hardell L, Eriksson M, Lenner P, et al. Malignant lymphomas and exposure to chemical agents, especially to organic solvents, chlorophenols and phenoxy acids. A case-control study. Br J Cancer 1981; 43: 169-176.

Harrington WJ, McAlister WH, Saltzstein SL, et al. A clinicopathologic conference on lymphoma or drug reaction occurring during hydantoin therapy for epilepsy. Am J Med 1962; 32: 286-297.

Henderson BE, Dworsky R, Pike MC, et al. Risk factors for nodular sclerosis and other types of Hodgkin's disease. Cancer Res 1979; 39: 4507-4511.

Hodgkin T. On some morbid appearances of the absorbent glands and spleen. Med Chir Trans 1832; 17: 68-114.

Holmes GKT, Stokes PL, Sorahan TM, et al. Coeliac disease, gluten free diet and malignancy. Gut 1976; 17: 612-619.

Hoover R. Hodgkin's disease in school teachers. N Engl J Med 1974; 291: 473.

Hoover R, Mason TJ, McKay FW, et al. Geographic patterns of cancer mortality in the U.S. In Persons at High Risk of Cancer. (Editor Fraumeni JF Jr). Academic Press, New York, 1975; 343-360.

Högstedt B. The micronucleus as an indicator of genotoxic exposure in man. Thesis. University of Lund, 1983.

IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Benzene, Lyon 1982; 29: 93-148.

Inman RD. Immunologic sex differences and the female predominance in systemic lupus erythematosus. *Arthritis and Rheumatism* 1978; 21:7: 849-852.

Jagar S, Kremer J, van Slochteren-Draaisma T. Presence of sperm agglutinating antibodies in infertile men and inhibition of in vitro sperm penetration into cervical mucus. *Int J Androl* 1979; 2: 117.

Kaplan HS. Hodgkin's disease. Harvard University Press, London, England, 1980; 236-279.

Kerzin-Storarr L, Faed MJW, Mac Gillivray JB, et al. Incidence of familial Hodgkin's disease. *Br J Cancer* 1983; 47: 707-712.

Kinlen LJ, Shiel AGR, Peto J, et al. A collaborate study of cancer in patients who have received immunosuppressive therapy. *Br Med J* 1979; 2: 1461-1466.

Kleinbaum D, Kupper L, Morgenstern H. Epidemiologic research - principles and quantitative methods . Lifetime Learning Publication, Belmont, California, 1982; p. 183-280.

Kolodny RC, Jacobs LS, Masters WH, et al. Plasma testosterone and semen analysis in male homosexuals. *N Engl J Med* 1971; 285: 1170-1174.

Kolodny RC, Jacobs LS, Masters WH, et al. Plasma gonadotrophins and prolactin in male homosexuals. *Lancet* 1972; ii: 18-20.

Krikorian JG, Burke JS, Rosenberg SA, et al. Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. *N Engl J Med* 1979; 300: 452-458.

Kvale G, Höiby EA, Pedersen E. Hodgkin's disease in patients with previous infectious mononucleosis. *Int J Cancer* 1979; 23: 593-597.

- Lang DJ, Kummer JF. Demonstration of cytomegalovirus in semen. *N Engl J Med* 1972; 287: 756-758.
- Langaney A, Pison G. Rougeole et augmentation temporaire de la masculinité des naissances: coincidence ou causalité. *C R Acad Sci (D)*, Paris, 1979; 289: 1255-1258.
- Lennert K, Mohri N, Stein H, et al. Malignant lymphomas other than Hodgkin's disease. Springer Verlag. Berlin, Heidelberg and New York, 1978.
- Le Shan L, Marvin S, Lysterly O. Some evidence of a relationship between Hodgkin's disease and intelligence. *Arch Gen Psych* 1959; 1: 477-479.
- Li FP, Fraumeni JF Jr, Mantel N, et al. Cancer mortality among chemists. *JNCI* 1969; 43: 1159-1164.
- Louie S, Daoust PF, Schwartz RS. Immunodeficiency and the pathogenesis of non-Hodgkin's lymphoma. *Semin Oncol* 1980; 7: 267-284.
- Louie S, Schwartz RS. Immunodeficiency and the pathogenesis of lymphoma and leukemia. *Semin Hematol* 1978; 15: 117-138.
- Mac Mahon B. Epidemiologic evidence on the nature of Hodgkin's disease. *Cancer* 1957; 10: 1045-1054.
- Mac Mahon B. Epidemiology of Hodgkin's disease. *Cancer Res* 1966; 26: 1189-1200.
- Mac Sween RNM. Reticulum cell sarcoma and rheumatoid arthritis in a patient with XY/XXY/XXX/Y Klinefelter's syndrome and normal intelligence. *Lancet* 1965; 1: 460.
- Matas AJ, Simmons RL, Najarian JS. Chronic antigen stimulation, herpes virus infections, and cancer in transplant recipients. *Lancet* 1975; 1: 1277-1279.
- Mc Farlin DE, Strober W, Waldmann TA. Ataxia-teleangiectasia. *Medicine* 1972; 51: 281-314.
- McMichael AJ, Andjelkovic DA, Tryoler HA. Cancer mortality among rubber workers: an epidemiologic study. *Annals NY Acad Sci* 1976; 271: 125-136.

Metroka CE, Cunningham-Rundles S, Pollack M, et al. Generalized lymphadenopathy in homosexual men. *Ann Intern Med* 1983; 99: 585-591.

Miller RW, Beebe GW. Infectious mononucleosis and the empirical risk of cancer. *JNCI* 1973; 50: 315-321.

Milham S Jr, Hesser JE. Hodgkin's disease in woodworkers. *Lancet* 1967; ii: 136.

Milham S Jr. Hodgkin's disease as an occupational disease of schoolteachers. *N Engl J Med* 1974; 290: 1329.

Milham S Jr. Nasal adenocarcinoma in woodworkers. *Lancet* 1967; i: 623.

Mitelman F, Brandt L, Nilsson PG. Relation among occupational exposure to potential mutagenic/carcinogenic agents, clinical findings and bone marrow chromosomes in acute nonlymphocytic leukemia. *Blood* 1978; 52: 1229-1237.

Mitelman F, Nilsson PG, Brandt L, et al. Chromosome pattern, occupation and clinical features in patients with acute nonlymphocytic leukemia. *Cancer Genetics and Cytogenetics* 1981; 4: 197-214.

Monson RR, Fine LJ. Cancer mortality and morbidity among rubber workers. *JNCI* 1978; 61: 1047-1053.

Monson RR, Nakano KK. Mortality among rubber workers. *Am J Epidemiol* 1976; 103: 297-303.

Morrow RH. Burkitt's lymphoma. In *Cancer Epidemiology and Prevention*. (Editors Schottenfeld D, Fraumeni JF). W B Saunders Company, Philadelphia, 1982; 739-753.

Muñoz N, Davidson RJL, Witthoff B, et al. Infectious mononucleosis and Hodgkin's disease. *Int J Cancer* 1978; 22: 10-13.

Mäki-Paakanen J, Husgafvel-Pursiainen K, Kalliomäki PL, et al. Toluene-exposed workers and chromosome aberrations. *J Toxicol Environ Health* 1980; 6: 775.

NCI (National Cancer Institute) Carcinogenesis Technical Report. Series No. 20: Bioassay of dapsone for possible carcinogenicity. DHEW Publication No. (NIH)77-820. Washington, D.C., U.S. Government Printing Office, 1977; pp vii-viii.

Newell G, Rawlings W, Kinnear BL, et al. Case-control study of Hodgkin's disease. I. Results of the interview questionnaire. JNCI 1973; 51: 1437-1441.

Nishiyama H, Anderson RE, Ishimaru T, et al. The incidence of malignant lymphoma and multiple myeloma in Hiroshima and Nagasaki atomic bomb survivors, 1945-1965. Cancer 1973; 32: 1301-1309.

Olin GR, Ahlbom A. The cancer mortality among Swedish chemists graduated during three decades. Environ Res 1980; 22: 154-169.

Olin R. Leukemia and Hodgkin's disease among Swedish chemistry graduates. Lancet 1976; ii: 916.

Olsson H, Brandt L. Asbestos exposure and non-Hodgkin's lymphoma. The Lancet 1983; March 12, 588.

Olsson H, Brandt L. Non-Hodgkin's lymphoma of the skin and occupational exposure to herbicides. The Lancet 1981; Sept. 12, 579.

Olsson H, Brandt L. Sex ratio in offspring of patients with non-Hodgkin's lymphoma. N Engl J Med 1982; 306: No. 6, 367-368.

Olsson H, Kristoffersson U. Tumor disease and heredity in females. Clin Gen 1983; 24: 292.

Petersen GR, Milham S Jr. Hodgkin's disease mortality and occupational exposure to wood. JNCI 1974; 53: 957-958.

Rappaport H. Tumors of the hematopoietic system. In Atlas of Tumor Pathology, section 3, Fasc 8. Washington D.C. Armed Forces Institute of Pathology, 1966; 1-442.

Razis DV, Diamond HD, Craver LF. Familial Hodgkin's disease: its significance and implications. Ann Int Med 1959; 51: 933-971.

Renard P, Celers J. Viral infections with urogenital manifestations. In Clinical virology. (Editors Debré R, Celers J). W B Saunders Company, Philadelphia, 1970; 705-714.

Registrar General for England and Wales: The Registrar General's Decennial Supplement for England and Wales, 1951. Occupational mortality, Part II, Vol 2. London, HMSO, 1958.

Registrar General for England and Wales: The Registrar General's Decennial Supplement for England and Wales, 1961. Occupational mortality tables. London, HMSO, 1971.

Registrar General for England and Wales: The Registrar General's Decennial Supplement for England and Wales, 1970-1972. Occupational mortality tables. London, HMSO, 1978.

Rosdahl N, Larsen SO, Clemmesen J. Hodgkin's disease in patients with previous infectious mononucleosis: 30 years experience. Br Med J 1974; 2: 253-256.

Rosenberg SA. Report of the committee on the staging of Hodgkin's disease. Cancer Res 1966; 26: 1310.

Ross R, Nichols P, Wright W, et al. Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. Lancet 1982; ii: 1118-1120.

Roubinian J, Talal N, Siiteri P, et al. Sex hormone modulation of auto-immunity in NZB/NZW mice. Arthritis Rheum 1979; 22: 1162-1169.

Schneider R. Comparison of age- and sex-specific incidence rate patterns of the leukemia complex in the cat and the dog. JNCI 1983; 70: 971-977.

Schwartz RS. Immunoregulation, oncogenic viruses, and malignant lymphomas. Lancet 1972; 1: 1266-1269.

Searle CE. Epidemiological study of the mortality of British cehmists. Br J Cancer 1978; 38: 192-193.

Smith PR, Lickiss JN. Benzene exposure and lymphoma. Lancet 1980; ii: 719.

Snider WD, Simpson DM, Aronyk KE, et al. Primary lymphoma of the nervous system associated with acquired immunodeficiency syndrome. *N Engl J Med* 1983; 308: 45.

Spector BD, Perry GS, Kersey JH. Genetically determined immunodeficiency diseases (GDID) and malignancy. Report from the Immunodeficiency-Cancer Registry. *Clin Immunol Immunopathol* 1978; 11: 12-16.

Steinberg AD, Melez KA, Raveche ES, et al. Approach to the study of the role of sex hormones in autoimmunity. *Arthritis Rheum* 1979; 22: 1170-1176.

Tabershaw IR, Cooper WC. A mortality study of petroleum refinery workers. Medical Research Report No. EA7402, prepared for the American Petroleum Institute by Tabershaw/Cooper Assoc, Inc, Berkely, California, Sept, 1974.

Thomas TL, Waxweiler RJ, Moure-Eraso R, et al. Mortality patterns among workers in three Texas oil refineries. *JOM* 1982; 24: 2: 135-145.

Thorell JI, Larsson SM. Radioimmunoassay and related techniques. Saint Louis, CV Mosby Co, 1978; 147-158.

Vessey MP. Epidemiological studies of the occupational hazards of anaesthesia. A review. *Anaesthesia* 1978; 33: 430-438.

Vianna NJ, Greenwald P, Davies JNP. Extended epidemic of Hodgkin's disease in high school students. *Lancet* 1971; i: 1209-1211.

Vianna NJ, Polan AK. Epidemiologic evidence for transmission of Hodgkin's disease. *N Engl J Med* 1973; 10: 499-502.

Vianna NJ, Polan A. Lymphomas and occupational benzene exposure. *Lancet* 1979; i: 1394-1395.

Vigersky RA, Chapman RM, Berenberg J, et al. Testicular dysfunction in untreated Hodgkin's disease. *Am J Med* 1982; 73: 482-486.

Waldmann TA, Strober W, Blaese RM. Immunodeficiency disease and malignancy: various immunological deficiencies in man and the role of immune processes in the control of malignant disease. *Ann Intern Med* 1972; 77: 605-628.

Wertheimer N, Leper E. Electrical wiring configurations and childhood cancer. *Am J Epidemiol* 1979; 109: 273-284.

Whorton D. Field studies: Lessons learned. *Teratogenesis, carcinogenesis and mutagenesis* 1984; 4: 25-44.

Ziegler JL, Drew WL, Miner RC, et al. Outbreak of Burkitt's like lymphoma in homosexual men. *Lancet* 1982; 2: 631-633.

Occupational handling of chemicals preceding Hodgkin's disease in men

In 1976 Olin¹ reported an increased death rate from Hodgkin's disease (HD) among Swedish chemistry graduates. We report an unduly high prevalence of occupations characterised by the handling of chemicals in men with HD.

Material, methods, and results

From tables describing the occupations of the working population of Sweden² we selected occupations indicating a high degree of exposure to chemicals (see table).

Patients—We examined the case records of all men aged 20-65 years (median 36) diagnosed and treated for HD during 1973-8 at this department and recorded their occupations at diagnosis, ages, and histological classifications. We thus studied 88 patients.

Controls—Control patients comprised three groups. In group A the case records of 100 consecutive men aged 20-65 years (median 43) with non-malignant disorders treated at the department of internal medicine in 1977 were examined and occupations recorded. In group B the case records of 100 consecutive men aged 20-65 years (median 39) treated at the department of allergology in 1977 were examined in the same way. In group C the occupations of 32 men in the same age group (median 52) with chronic leukaemias (10 with chronic lymphocytic and 22 with chronic myeloid leukaemia) seen during 1969-77 at the department of internal medicine were recorded. The recording of occupation was similar in all departments. Because only men aged 20-65 years were included in the study an occupation was obtained for all the patients and controls.

Of the 88 men with HD, 17 (19%) had occupations indicating that they handled chemicals (table). The corresponding figures in the two control groups with non-malignant disorders (A and B) were 2% and 3% respectively. This difference between the patients with HD and each of the control groups was significant ($P=0.0001$ and 0.0002 ; Fisher's exact probability test). Of the men with chronic leukaemias (group C), one (3%) had an occupation indicating handling of chemicals. This was also significantly different from the patients with HD ($P=0.02$). In Sweden in 1976² about 64 000 out of 2.2 million working men (2.9%) had occupations listed in the table.

Only two out of 35 patients (6%) aged 20-30 years were occupationally exposed to chemicals, compared with eight out of 31 (26%) aged 31-50 years. The corresponding proportion for the patients aged over 50 years was seven out of 22 (32%). Histological classification did not differ significantly between the exposed and unexposed patients.

Department of Oncology, University Hospital, S-221 85 Lund,
Sweden

H OLSSON, MD, research fellow

L BRANDT, MD, associate professor of internal medicine

Comment

Of the men with HD, which was diagnosed between 20 and 65 years of age, about 20% had occupations indicating that they handled chemicals. In the three control groups the corresponding figure was only 2-3%, which agrees well with the prevalence (2.9%) of such

Numbers of patients with occupations indicating high degree of exposure to chemicals in 88 men with Hodgkin's disease (HD) and three control groups. (See text for description of controls)

	Patients with HD (n = 88)	Control groups		
		A (n = 100)	B (n = 100)	C (n = 32)
Chemists	2		1	1
Painters and sprayers .. .	5	1	1	
Glass and pottery workers .. .	5			
Chemical processing workers .. .	1			
Rubber product workers .. .	2			
Plastics workers .. .	1		1	
Photographic laboratory workers .. .	1	1		

occupations in the working male population in Sweden. The results therefore suggest that exposure to some chemical agents may be important for the development of HD.

Interestingly, occupational exposure was uncommon in the patients with HD aged 20-30 years, whereas among the older patients 26-32% were occupationally handling chemicals. The incidence curve of HD is bimodal, with one peak between 20 and 30 years of age and a second increase beginning about the age of 35 years. This may be due to differences in aetiology between various age groups.³ Our results indicate that occupational exposure to chemical oncogenic agents may be of some importance for the development of HD in men aged over 30, whereas other aetiological factors may be more important in the younger age groups.

We emphasise that occupational titles obtained from case records will give only crude and insufficient information on occupational hazards. Despite this shortcoming, our finding of occupational exposure to chemicals in about 20% of adult men with HD means that efforts should be made to define environmental hazards that may be important in the development of HD. Such studies are in progress at our department.

This work was supported by grants from the Swedish Cancer Society.

¹ Olin, R, *Lancet*, 1976, **2**, 916.

² *Statistical Abstract of Sweden 1976*, vol 63. Stockholm, National Central Bureau of Statistics, 1976.

³ MacMahon, B, *Cancer Research*, 1966, **26**, 1189.

(Accepted 27 June 1979)

Occupational exposure to organic solvents and Hodgkin's disease in men

A case-referent study

by Håkan Olsson, MD, Lars Brandt, MD¹

OLSSON H, BRANDT L. Occupational exposure to organic solvents and Hodgkin's disease in men: A case-referent study. *Scand j work environ health* 6 (1980) 302—305. A standardized personal interview schedule was used to study occupational exposure to organic solvents among 25 men aged 20—65 a with Hodgkin's disease and 50 referents matched for sex, age and residence. When exposure was defined as the handling of organic solvents every workday for at least 1 a within the 10-a period immediately preceding the interview, 12 of the Hodgkin's disease patients (48 %) and six referents (12 %) were occupationally exposed with a relative risk of 6.6 ($p = 0.0005$). For 9 of the 12 exposed Hodgkin's disease patients exposure to aromatic solvents was verified, and such exposure may well have occurred for the remaining three patients also. It was concluded that exposure to organic solvents may constitute an occupational risk with regard to Hodgkin's disease.

Key terms: aromatic solvents, occupational hazard.

Results of epidemiologic studies suggest that occupational exposure to chemicals may be of etiologic importance for the development of Hodgkin's disease in men (4, 8, 9, 10, 11, 12). Among possible chemical agents, benzene has been pointed out as an occupational hazard with regard to malignant lymphoma, including Hodgkin's disease (2, 12). In the present report we present results from a case-referent study which indicate that exposure to other organic solvents may also be relevant to the development of Hodgkin's disease.

Hospital, Lund, with a recent diagnosis of Hodgkin's disease and aged 20—65 a were studied. All the patients were diagnosed in 1978 and 1979. Because exposure to occupational hazards rarely starts until the age of 20, younger patients were excluded from the study. It was also considered possible that the oldest patients might have difficulties to recall occupational exposure, and we therefore decided to exclude patients over the age of 65 from the study. Only one of the men admitted to our department with Hodgkin's disease during 1978—1979 was older than 65 a of age.

Subjects and methods

Patients

Twenty-five men admitted consecutively to the Department of Oncology, University

Referents

For each patient two referents were selected from the computerized Swedish population register. The referents were matched for sex and residence, and the two men closest in age to each respective Hodgkin's disease patient were selected. A letter was sent to the referents to inform them about the aim and organization of the investigation.

¹ Department of Oncology, University Hospital, Lund, Sweden.

Reprint requests to: Dr Håkan Olsson, Department of Oncology, University Hospital, S-221 85 Lund, Sweden.

Interviews

One investigator (HO) personally interviewed all the patients and referents. A questionnaire was drawn up and followed in order to standardize the interviews. The following interview schedule was used:

1. Occupations from school age up to the date of the interview were recorded. The period for each occupation and the name and address of the employer were registered.

2. A description was obtained of the various tasks during an average workday in each occupational period.

3. When handling chemicals was spontaneously mentioned as a work task, the interviewee was asked to define the chemicals used. He was also asked whether the handling of chemicals was sporadic or occurred every workday.

If the composition of the chemicals used was unknown, the employer and/or the manufacturer was contacted by letter for more information.

In addition to questions regarding occupation, those interviewed were asked about smoking and drinking habits.

No patient or referent refused to be interviewed. All the subjects were interviewed on one occasion except for one referent who was interviewed twice. One of the patients was an immigrant, and his occupational history was obtained through an interpreter.

Definition of exposure

Occupational exposure was defined as the handling of organic solvents every workday for at least 1 a within the closest 10-a period preceding the interview. In addition daily exposure for at least 1 a more than 10 a before diagnosis was recorded for the patients and referents.

Results

According to our definition 12 out of the 25 Hodgkin's disease patients (48 %) had been occupationally exposed to organic solvents. Six of the 50 referents (12 %) had been exposed (table 1). The relative

risk, calculated according to Miettinen (7), was 6.6 ($p = 0.0005$) with a 95 % confidence interval of 1.8–23.8. When the observation period was extended beyond the closest 10-a period, the same 12 patients (48 %) had been exposed, and 8 referents (16 %) had been exposed daily for at least 1 a.

The chemicals used by the exposed patients and referents are given in table 2. For nine of the patients exposure to aromatic hydrocarbons was recorded (patients 1–9). For the remaining three patients (patients 10–12) exposure to aromatic solvents could neither be confirmed nor precluded because the solvents used were only labeled by code.

The duration of exposure varied between 1.5–35 a with a median duration of 8 a (table 2). The time from the start of exposure to the diagnosis of Hodgkin's disease, ie, the latency period, was 4–35 a (median 10.5 a). For 8 of the 12 exposed patients the latency period was ≤ 15 a.

No differences in smoking or drinking habits were detected between the patients and referents.

Discussion

Our results are in agreement with other reports indicating that exposure to chemical agents may be of importance for the development of Hodgkin's disease in man (8, 9, 10, 11, 12). They suggest that organic solvents constitute a group of chemicals that are especially hazardous in this respect.

Although the personal interviews with the patients and referents were standardized, it was considered possible that the patients might be more motivated than the

Table 1. Exposure in triplets of patients and controls.

	Both referents exposed	One referent exposed	No referent exposed
Patient exposed	—	3	9
Patient not exposed	—	3	10

Table 2. Exposure of patients and referents to organic solvents. The numbers given to patients and referents are used for description in the text and do not indicate matched triplets.

Number	Age (a)	Occupation	Solvents	Duration of exposure (a)
<i>Patients</i>				
1	36	Chemist	Xylene, trichloroethylene	14
2	46	Wood fiber worker	Toluene, xylene, styrene, phenol	15
3	51	Painter	Toluene, various coded paints and solvents	35
4	27	Chemist, varnish research	Toluene, xylene, hexane, tetrahydronaphthalene, ethyl acetate, cyclohexane, white spirit ^a	4
5	27	Electrician, cleaning transformers.	Toluene, hexane, trichloroethylene, trichloroethane, glycol ether	5
6	48	Plastics worker	Styrene, cellulose acetate	9
7	36	Printer	Toluene, coded solvents	20
8	56	Painter	Toluene, xylene, various coded solvents	7
9	45	Repair and cleaning of typewriters	Trichloroethylene, white spirit ^a	29
10	21	Painter	Various coded paints and solvents, cellulose glues	1.5
11	39	Fuel production for model air crafts	Various coded solvents, methanol	5
12	59	Chemical process worker	Various coded solvents, ethanol	7
<i>Referents</i>				
1	46	Pharmacist	Various solvents, other chemicals	26
2	45	Woodworker, making wooden shoes	Acetone, various glues	3
3	36	Shipyard worker	Toluene, various coded paints and solvents	10
4	29	Painter	Toluene, various coded paints and solvents	6
5	28	Printer	Toluene, various coded solvents	12.5
6	23	Photographer	Hydroquinone, p-aminophenol	1

^a May contain ≤ 17 % aromatic hydrocarbons.

referents to answer questions and to recall exposure. To reduce this bias, we required a period of 1 a of daily handling solvents to define exposure. Moreover, we considered that all those interviewed should be able to recall such a long period if it had occurred during the last 10 a. Admittedly, exposure to solvents for shorter periods than 1 a might be of importance for the development of Hodgkin's disease, and exposure to solvents may therefore be of an even greater etiologic importance for Hodgkin's disease than is indicated by our results.

Vianna & Polan (12) suggested that occupational exposure to benzene will in-

crease the risk of Hodgkin's disease, but they also stated that exposure to other organic solvents might be of some importance. Exposure to benzene was not recorded for any of our patients. Because many of the solvents used were only designated by codes or had commercial names, we were sometimes unable to determine their composition. In Sweden benzene became a classified poison in 1972, and it is therefore unlikely that in recent years benzene was added to commercial solvents.

The occupational handling of various aromatic solvents was documented for 9 of the 12 exposed Hodgkin's disease pa-

tients but may well have occurred for all of them. Commercially available aromatics may contain benzene as an impurity (5), and it is possible that exposure to at least small amounts of benzene was common. It cannot therefore be established whether several aromatic solvents are hazardous with regard to Hodgkin's disease or whether the oncogenic effect of these solvents is due to benzene as an impurity. In either case exposure to commercial aromatic solvents may constitute an occupational risk with regard to Hodgkin's disease.

In addition to the handling of aromatic hydrocarbons, the handling of other organic solvents was common in the group of exposed patients. It is possible therefore that exposure to organic solvents may be relevant for the development of Hodgkin's disease, irrespective of the chemical configuration.

The median duration of exposure to solvents was 8 a for the Hodgkin's disease patients. In patients with acute myeloid leukemia following exposure to benzene, the corresponding time was an average of 10 a (1) and for six Hodgkin's disease patients exposed to benzene the mean duration of exposure was 11 a (2). A relatively short period of exposure to oncogenic chemicals may therefore be sufficient to promote the development of malignancy in hemopoietic or lymphoid tissue. The median latency period, ie, the time from the start of occupational exposure to the diagnosis of Hodgkin's disease, was also relatively short, 10.5 a. For two-thirds of the patients the latency period was ≤ 15 a.

For the present study men of working age, ie, 20–65 a of age, were selected. In Sweden one-third of the men with Hodgkin's disease in this age group are 20–34 a old at diagnosis and two-thirds are 35–64 a (3). For Hodgkin's disease there is a bimodal age incidence curve with one peak between 25–30 a of age and a second increase beginning at about the age of 35 a. It has been proposed that this phenomenon may indicate differences in etiology between Hodgkin's disease in younger and older age groups (6). Of our 12 Hodgkin's disease patients exposed to

solvents, three were 20–34 a old and nine were 35 a or over. Thus it is possible that exposure to organic solvents may promote the development of Hodgkin's disease irrespective of other, still unknown, etiologic factors.

Acknowledgments

We wish to thank T Möller, MD, and B Gullberg, PhD, of the Tumor Registry for Southern Sweden for their assistance with the selection of the referents and their valuable statistical advice.

This work was supported by grants from the Swedish Cancer Society.

References

1. Aksoy M, Erdem S, Dincol G. Types of leukemia in chronic benzene poisoning: A study in thirty-four patients. *Acta haematol* 55 (1976) 65–72.
2. Aksoy M, Erdem S, Dincol K, Hepyüksel T, Dincol G. Chronic exposure to benzene as a possible contributory etiologic factor in Hodgkins disease. *Blut* 28 (1974) 293–298.
3. Cancer Registry, National Board of Health and Welfare. Cancer incidence in Sweden 1973. Stockholm 1979.
4. Greene MH, Hoover RW, Eck RL, Fraumeni JF. Cancer mortality among printing plant workers. *Environ res* 20 (1979) 66–73.
5. Hunter D. The diseases of occupations. The English Universities Press Ltd, London 1969, p 507.
6. MacMahon B. Epidemiology of Hodgkin's disease. *Cancer res* 26 (1966) 1189–1200.
7. Miettinen OS. Estimation of relative risk from individually matched series. *Biometrics* 29 (1970) 75–86.
8. Olin R. Leukaemia and Hodgkin's disease among Swedish chemistry graduates. *Lancet* 2 (1976) 916.
9. Olin R. The hazards of a chemical laboratory environment — A study of the mortality in two cohorts of Swedish chemists. *Am ind hyg assoc j* 39 (1978) 557–562.
10. Olin R, Ahlbom A. The cancer mortality among Swedish chemists graduated during three decades: A comparison with the general population and with a cohort of architects. *Environ res* (1980) 154–161.
11. Olsson H, Brandt L. Occupational handling of chemicals preceding Hodgkin's disease in men. *Br med j* 2 (1979) 580–581.
12. Vianna NJ, Polan A. Lymphomas and occupational benzene exposure. *Lancet* 1 (1979) 1394–1395.

PRELIMINARY REPORT

Supradiaphragmatic Presentation of Non-Hodgkin's Lymphoma in Men Occupationally Exposed to Organic Solvents

H. Olsson and L. Brandt

From the Department of Oncology, University Hospital, Lund, Sweden

ABSTRACT. Using a standardized interview schedule, occupational exposure to organic solvents was investigated in 61 consecutive male patients with the diagnosis of non-Hodgkin's lymphoma. When exposure was defined as handling of organic solvents every working day for at least one year, 23 patients were exposed and 38 non-exposed. Of 15 patients with clinical stage I–II above the diaphragm, 12 (80%) were occupationally exposed to organic solvents. Only 1 (11%) of 9 patients with clinical stage I–II disease located below the diaphragm was exposed. Thirty-seven patients had clinical stage III–IV disease at the time of diagnosis and 10 (27%) of these were exposed. The predominance of exposed patients in the group with stage I–II disease above the diaphragm is significant and the results indicate a relation between exposure to organic solvents and supradiaphragmatic presentation of non-Hodgkin's lymphoma. No correlation was found between exposure and the morphology of the lymphomas.

Key words: non-Hodgkin's lymphoma, occupational exposure, organic solvents.

Acta Med Scand 210: 415, 1981.

Occupational exposure to organic solvents has been found to be related to the development of Hodgkin's disease (7, 10, 13) and non-Hodgkin's lymphoma (NHL) (7, 13). The purpose of this study was to investigate whether previous occupational exposure to organic solvents is associated with any particular clinical or morphologic characteristics of NHL.

PATIENTS

A consecutive series of 61 male patients with NHL referred to our department from Oct. 1978 through Sept. 1980 for diagnosis and clinical staging was studied. Their age was 29–81 years (mean 58.2).

MATERIAL AND METHODS

Morphologic classification and staging procedures. Representative tumour material was obtained from all patients by biopsy and classified according to Rappaport (12). For the purpose of the present study the lymphomas were divided into three morphological groups: lymphocytic, mixed cell type and histiocytic.

Clinical staging according to the Ann Arbor classification (3) was based on physical examination, chest X-ray, lymphangiography and abdominal CT scan. In addition to biopsy from a representative lymph node or from extranodal lesions, fine-needle aspiration biopsies were taken from palpable lymph nodes and from lymph nodes with questionable abnormal size or structure visualized on lymphangiography or CT scan. Bone marrow biopsy from the iliac crest was obtained from all patients and peripheral blood smears were examined in all. Multiple biopsies from Waldeyer's ring were obtained from all patients. Diagnostic laparotomy was performed only occasionally but fine-needle aspiration biopsies were taken from the liver and spleen of all patients.

According to the results of the staging procedures, the patients were divided into three categories: Stage I–II lymphoma located above the diaphragm, stage I–II located below the diaphragm, and stage III–IV. Four patients with extranodal visceral involvement as the primary manifestation were referred to the last category.

Interviews and definition of exposure. All patients were interviewed personally by one of us (H.O.). A questionnaire described previously (10) was followed in order to standardize the interviews. The following schedule was used: 1) Occupations from school age up to the date of the interview were recorded. The period of each occupation and the name and address of the employer were registered. 2) Description of the various tasks during an average working day in each occupational period. 3) When handling of chemicals was spontaneously mentioned as a working task, the interviewee was asked to define the chemicals used. He was also asked whether he had handled chemicals sporadically or every working day. In case of unknown composition of the chemicals used, further information was requested by letter from the employer and/or the manufacturer. In addition to questions regarding occupation, the interviewees were asked about smoking and drinking habits.

Occupational exposure was defined as handling of organic solvents, aliphatic and aromatic, every working day

Table I. Location of NHL in exposed and non-exposed patients

	Stage I-II above diaphragm	Stage I-II below diaphragm	Stage III-IV
Exposed	12	1	10
Non-exposed	3	8	27

for at least one year. All interviews took place on admission to our clinic, i.e. before the result of the staging procedures was known.

RESULTS

Exposure to toluene was reported by 15 patients, xylene by 11, benzene by one, and other aromatic solvents by 10 patients. Various aliphatic solvents had been used by 7 patients. In most cases exposure to more than one chemical solvent was reported.

The numbers of exposed and non-exposed patients according to our definition and in the various stage categories are given in Table I. Out of 15 patients with stage I-II disease above the diaphragm at the time of diagnosis, 12 (80%) were exposed. The proportion of exposed patients in this group was larger than in the patients with stage I-II disease below the diaphragm, 1 out of 9 (11%), and also larger than the proportion of exposed patients presenting with stage III-IV disease, 10 out of 37 (27%). The predominance of exposed patients in the group with stage I-II disease above the diaphragm is significant ($\chi^2=15.9$, $p=0.0003$).

The mean ages of the exposed (55.2 years) and the non-exposed patients (59.9 years) did not differ significantly. The mean age of the patients with stage I-II disease above the diaphragm was 54.8, in those with stage I-II below the diaphragm 57.8 and in the patients with stage III-IV disease 59.6. The differences between the mean ages in each group are not significant. Smoking and drinking habits were similar in exposed and non-exposed patients.

The lymphomas were classified as lymphocytic in 10, mixed cell type in 6 and histiocytic in 7 of the exposed patients. The corresponding proportions in the non-exposed group were 13, 8 and 17, respectively. Thus there was no significant predominance of any particular morphologic type in the exposed patients when compared with the non-exposed.

DISCUSSION

The aim of this study was to investigate whether NHL patients with a history of occupational exposure to organic solvents present with some particular clinical or morphologic features. The results of clinical staging and histologic examination of lymphoma tissue were therefore recorded in a group of men exposed daily to organic solvents in their occupation for at least one year and compared to the corresponding findings in a group of men without such exposure. Information on exposure was obtained by standardized personal interviews. Because each interview was performed on admission, i.e. before staging procedures had been completed, the interviewer was unbiased with regard to the clinical stage of the disease. All patients interviewed had the same malignant disease, NHL, and it is therefore unlikely that any subgroup of patients was especially biased to recall exposure.

In a previous case-control study of exposure to solvents preceding Hodgkin's disease (10) we found that 16% of healthy men aged 20-65 living in our hospital region had occupationally handled organic solvents every working day for at least one year. According to the same definition, 23 (38%) of the present 61 NHL patients had been exposed. Because no matching controls were interviewed about exposure to solvents, we cannot evaluate the statistical significance of the large proportion of exposed men with NHL. However, the finding of a high-grade exposure in more than one third of a consecutive series of men with NHL may be in line with results from recent epidemiological studies demonstrating that exposure to organic solvents is a risk factor for development of NHL (2, 7, 13).

An association between occupational exposure to solvents and location of lymphoma above the diaphragm was observed at the diagnosis of NHL. The majority of patients with stage I-II disease located above the diaphragm (80%) were occupationally exposed to organic solvents whereas such exposure was uncommon among those with stage I-II below the diaphragm (11%). Exposure was also more common among patients with stage I-II disease above the diaphragm than among those with NHL stage III-IV (27%).

The age span of the patients studied was large, 29-81 years, and it was considered possible that young men are more often exposed to chemicals than the elderly. If NHL stage I-II located above the diaphragm is a typical finding in young NHL

patients, the positive association between exposure and supradiaphragmatic location of lymphomas should be expected. However, the mean ages of the exposed and non-exposed patients did not differ markedly. Moreover, the mean ages of the patients with stage I-II lymphoma above the diaphragm, of those with stage I-II disease below the diaphragm and of those with stage III-IV lymphoma were similar. A causal relationship between exposure to organic solvents and the presentation of NHL above the diaphragm in the exposed patients is therefore possible.

The largest proportion of exposed patients (80%) was found among patients with stage I-II lymphoma above the diaphragm. The lowest proportion, 11%, was found in stage I-II below the diaphragm. A frequency of 27% exposed patients was noted among those with stage III-IV disease. In patients presenting with stage III-IV lymphoma the primary location of the lymphoma is uncertain, and it is probable that the initial lesion was located above the diaphragm in some of them. If exposure to organic solvents is associated with an initially supradiaphragmatic location of the lesion in NHL, a somewhat larger proportion of exposed patients should be expected in stage III-IV than in stage I-II disease below the diaphragm. The intermediate frequency of exposure noted in stage III-IV is therefore compatible with the concept of a relation between exposure and initial location of lymphoma in NHL.

Since organic solvents are volatile, inhalation may cause a considerable exposure of the mucous membranes in the upper and lower respiratory tract. It is reasonable to assume that lymphoid tissue regional to these areas is exposed to higher concentrations of the substances than such tissue in other parts of the body. If some organic solvents promote the development of NHL, the initial lesion should be found in lymphoid tissue above the diaphragm rather than in lymphoid tissue located elsewhere.

Among organic solvents, benzene has a well documented oncogenic effect (1). Exposure to benzene was documented in only one of our patients. Moreover, the fact that this solvent was declared poison in Sweden in 1972 makes it unlikely that exposure to benzene was a common occupational hazard in the present series of patients. Vianna and Polan (13) suggested that occupational exposure to solvents other than benzene may also give rise to

the development of NHL. Toluene, commonly handled by the exposed patients, is generally considered a safe solvent substitute for benzene. There are, however, discrepancies in findings related to chromosomal aberrations in lymphocytes among workers exposed to toluene. Thus Funes-Cravioto et al. (6) reported an excess of lymphocyte sister chromatid exchanges in workers exposed to toluene. This finding was not confirmed by Mäkipää et al. (9). Toluene injected into animals may cause chromosome aberrations (8), and inhalation exposure may cause chromosome damage of long duration in rats (4). Moreover, toluene may enhance the carcinogenic effect of the polycyclic hydrocarbon DMBA (5). There is also evidence that local application of xylene will increase the yield of experimental tumours induced by the mutagenic substance urethane (11). Although aromatic solvents like toluene and xylene may not be carcinogenic per se, relatively high concentrations of such chemicals in lymphoid tissue might enhance the effect of oncogenic agents.

Various morphologic subtypes of acute leukemia may follow exposure to benzene (1). In the exposed NHL patients, no particular morphologic type of lymphoma predominated. It is therefore possible that exposure to organic solvents may be associated with various morphologic subtypes also in NHL.

REFERENCES

1. Aksoy, M., Erdem, S. & Dincol, G.: Types of leukemia in chronic benzene poisoning. A study in thirty-four patients. *Acta Haematol* 55: 65, 1976.
2. Cappuro, P. U.: Cancer in a community subject to air pollution by solvent vapors. *Clin Toxicol* 14: 285, 1979.
3. Carbone, P. P., Kaplan, H. S., Musshof, K., Smithers, D. W. & Tubiana, M.: Report of the committee on Hodgkin's disease staging. *Cancer Res* 31: 1860, 1971.
4. Dobrokhotov, V. B. & Enikoev, M. I.: The mutagenic action of benzol, toluol and mixture of these hydrocarbons in a chronic test. *Gig Sanit* 41: 32, 1976.
5. Frei, J. V. & Kingsley, W. F.: Observations on chemically induced regressing tumours of mouse epidermis. *J Natl Cancer Inst* 41: 1307, 1968.
6. Funes-Cravioto, F., Kolmodin-Hedman, B., Lindsten, J. et al.: Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a photoprinting factory and in children of women of laboratory workers. *Lancet* 2: 322, 1977.
7. Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E.: Malignant lymphomas and exposure to chemical

- agents, especially to organic solvents, chlorophenols and phenoxy acids. *Br J Cancer* 43: 169, 1981.
8. Lyapkalo, A. A.: Genetic activity of benzene and toluene. *Gig Tr Prof Zabol* 17: 24, 1973.
9. Mäki-Paakkanen, J., Husgafvel-Pursiainen, K., Kalliomäki, P. L., Tuominen, J. & Sorsa, M.: Toluene-exposed workers and chromosome aberrations. *J Toxicol Environ Health* 6: 775, 1980.
10. Olsson, H. & Brandt, L.: Occupational exposure to organic solvents and Hodgkin's disease in men. A case-control study. *Scand J Work Environ Health* 6: 302, 1980.
11. Pount, A. W. & Withers, H. R.: The influence of some irritant chemicals and scarification on tumour initiation in mice. *Br J Cancer* 17: 460, 1963.
12. Rappaport, H.: Tumours of the hematopoietic system. In: *Atlas of tumor pathology*, sect. 3, fasc. 8, pp. 97-161. Armed Forces Institute of Pathology, Washington D.C. 1966.
13. Vianna, N. J. & Polan, A.: Lymphomas and occupational benzene exposure. *Lancet* 1: 1394, 1979.

IMPAIRED TESTICULAR FUNCTION IN A SUBGROUP
OF MEN WITH MALIGNANT LYMPHOMA

H. Olsson¹, MD, L. Brandt¹, MD, J. Ranstam², B Sc,
and M. Bjerström³, Lab techn

¹Department of Oncology, ²Southern Swedish Regional Tumour Registry and

³Department of Forensic Medicine, University Hospital, S-221 85 Lund,
Sweden

SUMMARY

Lifetime occupational histories were obtained from 57 consecutive adult men with a recent diagnosis of non-Hodgkin's lymphoma or Hodgkin's disease. For 23 patients a daily occupational exposure to organic solvents for at least one year was recorded. There is epidemiological evidence that such exposure may increase the risk of malignant lymphoma and it was therefore considered probable that for some of the patients, exposure to these chemicals was of etiologic importance. For the remaining 34 patients other, as yet unidentified etiologic factors are likely to be more important. In the exposed group P-testosterone and S-luteinizing hormones (S-LH) were essentially normal. In the unexposed group reduced P-testosterone and elevated levels of S-LH were observed, indicating a gonadal insufficiency. Semen analyses in a group of 13 exposed patients were normal whereas in another group of 20 unexposed men the concentration of sperm cells was sub-normal and the ability to penetrate ovalbumen impaired. The differences in hormone levels and semen characteristics were not due to differences in clinical stage, histology or the presence of B-symptoms. The results indicate that the testicular function is impaired in some male lymphoma patients for whom the etiology is entirely unknown. Some agent(s) initiating a lymphoproliferative disorder may also affect the testicular function. An alternative explanation of the results is that men with a gonadal insufficiency run an increased risk of lymphoma.

INTRODUCTION

It is probable that various agents are of etiologic importance in malignant lymphoproliferative disorders. Results of epidemiologic studies suggest that occupational exposure to chemicals, e.g. organic solvents^{1,2,3}, herbicides³ and asbestos⁴, may be of importance in some cases whereas in most patients no environmental hazards can be identified. In an attempt to define clinical characteristics in men with lymphoma and previous heavy exposure to organic solvents we have compared these patients with male lymphoma patients without such exposure. The comparison comprises histology, location of initial lesion, clinical stage and various biochemical analyses including assays of sex hormones. The results of the hormone assays indicate that the gonadal function is normal in men for whom occupational exposure to organic solvents may be of etiologic importance whereas signs of an impaired gonadal function were observed in those without any prolonged exposure to environmental hazards. Because of these differences the study has been extended to include semen analyses. We report here results

indicating that an impaired testicular function is characteristic in the subgroup of men with malignant lymphoma for whom the etiology is entirely unknown.

METHODS

Patients

Assays of sex hormones were performed in 57 consecutive untreated men with malignant lymphoma. Thirty-seven had non-Hodgkin's lymphoma (NHL) and 20 had Hodgkin's disease (HD). The median age was 51 years, range 17-80 years.

Semen analyses were performed in 33 untreated patients, 18 with NHL and 15 with HD. The median age was 41 years, range 20-65 years.

Controls

Semen was analysed prior to vasectomy in 114 apparently healthy fertile men aged 27-52, median age 36.

Hormone analyses

Blood samples were drawn at 8 00 a.m. P-testosterone, S-luteinizing hormone (S-LH) and S-follicle stimulating hormone (S-FSH) were analysed at the Department of Clinical Chemistry, Malmö General Hospital, with radioimmunoassay technique⁵. Normal reference values for P-testosterone were 6-30 nmol/l, S-LH 0.5-3.0 µg/l and S-FSH 0.5-2.5 µg/l.

Semen analyses

Semen was collected by masturbation after at least three days of sexual abstinence. Volume of ejaculate, sperm concentration in millions per ml and percentage of motile, dead and normal sperm cells were recorded. The percentages of sperms with various morphologic abnormalities were assessed and the admixture of leukocytes estimated. In addition motility in a capillary tube and penetration in hen's ovalbumen were determined. The semen analyses were performed prior to diagnostic procedures which could affect sperm function, e.g. operation with anaesthesia. No patient was treated with corticosteroids or other drugs known to affect the gonadal function.

Morphologic classification and staging procedures

In all patients representative tumour material was obtained through biopsy

and classified according to Rappaport⁶ or Rye⁷. Clinical staging according to the Ann Arbor system⁸ was based on physical examination, chest X-ray, lymphangiography, abdominal CT-scan and scintigraphy of the liver and spleen. In addition to biopsy from a representative lymph node or from extranodal lesions, fine-needle aspiration biopsies were obtained from lymph nodes with questionable abnormal size or structure visualized on lymphangiography or CT-scan and from the liver and spleen. Bone marrow biopsies from the iliac creast were performed in all patients and peripheral blood smears were examined in all. Multiple biopsies from Waldeyer's ring were obtained in all patients. Diagnostic laparotomy was performed in the HD patients with tumour stage I-II but not in those with NHL. The presence or absence of B-symptoms was recorded in each patient.

Other clinical and biochemical analyses

Height and weight were registered. The liver enzymes gamma glutamyl transferase, alkaline phosphatase and lactate dehydrogenase were assessed and the patients were questioned about alcohol habits.

Occupational histories

Lifetime occupational histories were taken from all patients on admission according to a technique previously described². Each patient who had handled organic solvents every working day for at least one year prior to diagnosis was classified as exposed. All other patients were considered unexposed. The classification was made without knowledge of the results of the hormonal assays or sperm tests, because these analyses were performed 1-3 weeks after admission.

Statistical methods

After logarithmic transformation of the hormone values partial correlation coefficient, discriminant analysis (Wilk's method) and analysis of variance were used to investigate the interrelationship between the variables studied. Normally distributed variables needed for the analyses were derived by logarithmic transformations of the original values. Analysis of covariance and discriminant analysis were used to compare semen characteristics in the lymphoma patients and the controls.

RESULTS

Hormone analyses

Twenty-three of the fifty-seven patients had been exposed to organic solvents every working day for at least one year prior to diagnosis. Clinical data on exposed and unexposed patients are given in Table I. S-FSH was 2.80 ± 2.03 (SD) $\mu\text{g/l}$ in exposed patients compared to 3.06 ± 2.86 $\mu\text{g/l}$ in the unexposed group. The corresponding values for S-LH were 1.83 ± 1.04 and 2.19 ± 1.02 $\mu\text{g/l}$ (Fig 1) and for P-testosterone 17.11 ± 8.13 and 11.45 ± 3.85 nmol/l (Fig 2). The patients without occupational exposure to organic solvents had significantly lower P-testosterone ($p < 0.002$) and higher S-LH ($p < 0.05$) than the exposed patients after controlling for age, stage and NHL/HD. S-FSH was not significantly different in the two groups after controlling for the above factors ($p > 0.7$).

Older patients had higher S-FSH and S-LH values compared to younger ones ($p < 0.001$, $p < 0.001$ respectively). P-testosterone did not change significantly with age ($p > 0.05$), but there was a reduction associated with advanced tumour stage after controlling for age ($p < 0.02$). S-FSH and S-LH remained unchanged with regard to stage ($p > 0.1$).

In a discriminant analysis taking into consideration age of the patient, tumour stage, NHL/HD, histological subgroups, B-symptoms, S-FSH, S-LH, P-testosterone and one interaction term (stage x exposure), only P-testosterone ($p < 0.004$) and S-LH ($p < 0.08$) were found to be independent variables with respect to exposure to organic solvents. If P-testosterone was known, no further discrimination could be achieved by an analysis of S-LH ($p > 0.4$) suggesting that P-testosterone by itself was the true discriminator. After controlling for age and exposure, it was found that S-FSH, S-LH and P-testosterone did not differ between patients with NHL and HD.

There was no difference in alcohol consumption habits, weight indices or liver enzyme tests between the exposed and unexposed patients.

Occupational exposure to chlorophenols and herbicides could be confounding factors for the results³. Therefore occupational histories were reviewed with regard to such exposure. Six patients unexposed to solvents but with occupational exposure to chlorophenol or herbicides for various periods

had low P-testosterone values similar to other patients without exposure to organic solvents.

Semen analyses

The mean concentration of sperm cells was 35 millions/ml in 20 unexposed patients and significantly lower than in 13 exposed, 148 millions/ml ($p < 0.0004$). The concentration was also lower than in the controls, 96 millions/ml ($p < 0.001$). There was no significant difference in sperm concentrations between the exposed patients and the controls ($p = 0.11$, Fig 3). The significance of the difference between unexposed and exposed patients was calculated, controlling for age, stage of disease, B-symptoms and NHL/HD. Comparison of the patients and controls was performed controlling for age.

The ability of the spermatozoa to penetrate ovalbumen was determined in 18 unexposed patients, 12 exposed patients and 114 controls. In three patients, two unexposed and one exposed, the number of sperm cells was too small to permit this analysis. The normal reference value used in our laboratory is a penetration of >35 mm in two hours. In the unexposed group 13 of 18 patients (72 %) had a reduced ability to penetrate and in the exposed group the corresponding figures were 5 out of 12 (42 %). Among the 114 controls 25 (22 %) had a reduced ability to penetrate ovalbumen. A discriminant analysis controlling for age showed that the ability to penetrate was significantly lower in the unexposed patients compared to the controls ($p < 0.001$). The difference between exposed patients and controls was not significant ($p = 0.20$). Other qualities of the sperm cells studied did not differ in the two groups of lymphoma patients and the controls.

Table I. Clinical data in 23 exposed and 34 unexposed lymphoma patients

	Exposed (n=23)	Unexposed (n=34)
Age (yrs)	Median 52, range 20-74	Median 49, range 17-80
Stage III-IV	12 (52 %)	22 (65 %)
B-symptoms	4 (17 %)	10 (29 %)
HD	10 (43 %)	10 (29 %)
NHL	13 (57 %)	24 (71 %)

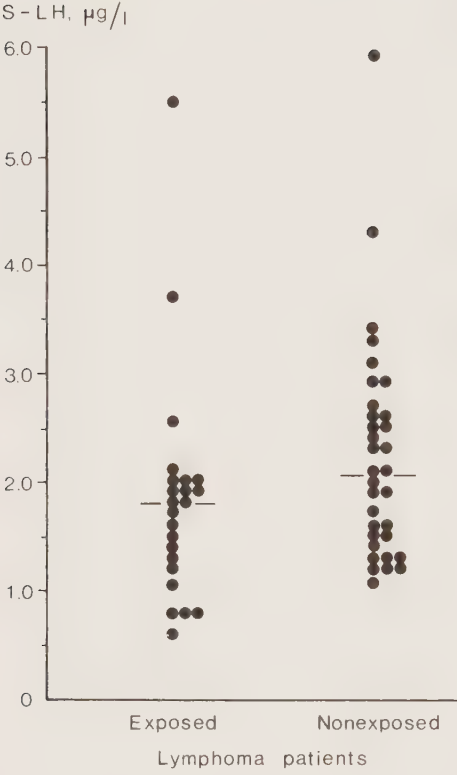


Fig 1. S-LH concentrations in exposed and unexposed patients

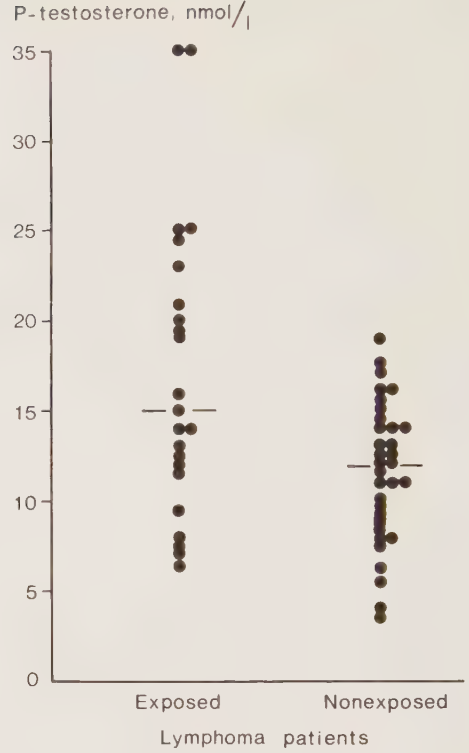


Fig 2. P-testosterone concentrations in exposed and unexposed patients

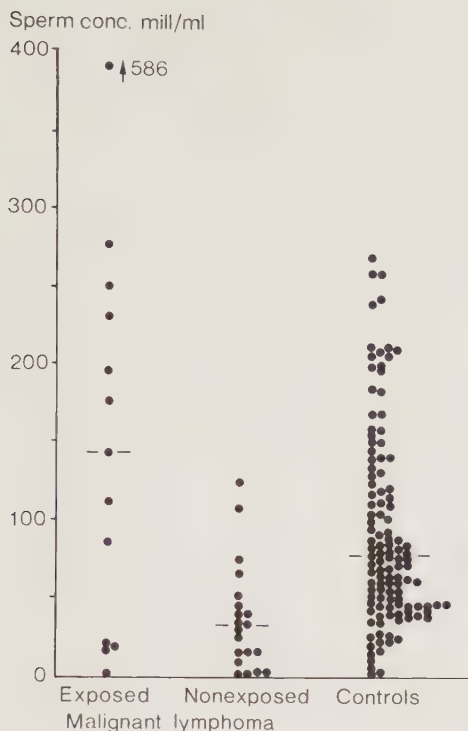


Fig 3. Concentration of sperm cells in semen from 13 exposed patients, 20 unexposed patients and 114 controls

DISCUSSION

In the present study the gonadal function was analysed in two categories of men with a recent diagnosis of malignant lymphoma. One group was studied because a thorough occupational history revealed a daily occupational exposure to organic solvents for at least one year preceding the development of lymphoma. Epidemiologic studies have indicated that such exposure may be associated with an increased risk of malignant lymphoma^{1,2,3} and it was therefore considered probable that for some patients in this group exposure to chemicals was of etiologic importance for their disease. A larger group comprised men without such exposure and in these patients other, yet unidentified etiologic factors were assumed to be more important. Assays of sex hormones and semen analyses showed that the exposed men had a normal gonadal function whereas the group of men with an entirely unknown etiology of the lymphomas had signs of an impaired testicular function.

In the unexposed group all P-testosterone values were in the low normal range or subnormal and significantly lower than in the group of exposed lymphoma patients. The average level of S-LH was higher in the unexposed than in the exposed patients. A discriminant analysis showed that the differences in P-testosterone and S-LH were not due to differences in age, clinical stage, histology or presence of B-symptoms and that the P-testosterone level was the best discriminator between the two groups of patients. There were no differences between unexposed and exposed patients regarding height and weight, liver function tests or alcohol consumption. Nor was handling of herbicides or chlorophenols a confounding factor explaining the differences observed between the patients exposed to organic solvents and those without such exposure. It was therefore considered probable that a relatively low testicular function may be characteristic for men with lymphoma caused by as yet unidentified factors.

The results of the sperm tests in unexposed and exposed men corresponded to the results of the sex hormone analyses. Thus the sperm concentration and the ability of the sperm to penetrate ovalbumen were subnormal in the group of men with entirely unknown etiology of their lymphoma and differed from the patients occupationally exposed to organic solvents. The results were not due to differences in age, clinical stage, histology or presence of constitutional symptoms.

The finding of a normal testicular function in the lymphoma patients exposed to potential mutagenic/carcinogenic chemicals indicates that lymphoma is not necessarily associated with an impaired gonadal function. It is therefore remarkable that the testicular function was subnormal in another group of patients with a similar age and with a comparable tumour burden and it must be considered that their impaired testicular function was not caused by their disease.

One possible interpretation of the present results is that some unknown agent(s) initiating a lymphoproliferative disorder may also affect the gonadal function in men. Some infectious agents might have such a dual effect. Viral infections are suspected of being of etiologic importance in malignant lymphoma⁹ and orchitis may follow infections with e.g. mumps and Coxsackie B viruses¹⁰. Titers of cytomegalovirus are considerably higher in semen than in other secretions¹¹.

There is experimental evidence that sex hormones may strongly influence immune responses¹². Therefore an alternative interpretation of the present results is that men with an acquired or congenital impairment of testicular functions are at risk of developing lymphoma. Such a concept is supported by experimental studies in NZB mice. Antigenic stimulation in these animals may cause an unrestricted proliferation of B-lymphocytes¹³ favouring the development of autoimmune conditions and B-cell malignancies and the mice are prone to die from such disorders¹⁴. If male NZB mice are castrated the mortality is greatly enhanced.

The administration of testosterone abrogates this effect of orchiectomy¹⁵. It has been proposed that in man too immunologic failure to regulate B-cell proliferation may favour the development of lymphoproliferative malignancies¹⁶, but to our knowledge the possible influence of a testicular dysfunction on immune regulatory mechanisms has not been evaluated in man. Certain groups of men may be of special interest in this respect. Thus ataxia teleangiectasia (AT) may be associated with a testicular dysfunction¹⁷. The major cause of death in AT is overwhelming infections related to an immunologic deficiency¹⁷. Moreover malignant lymphoproliferative disorders are unduly common in AT¹⁸. Some male homosexuals have a gonadal insufficiency with low P-testosterone levels, reduced sperm cell counts and elevated S-LH concentrations^{19,20}, whereas normal testicular function has been found in others^{21,22}. A minority among homosexual men may display a reduced cell-mediated immunity, susceptibility to opportunistic infectious agents and lymphadenopathy with a strikingly high incidence of malignant lymphoma²³. It might therefore be worth while to investigate whether those male homosexuals with a testicular dysfunction are at special risk of developing the acquired immunodeficiency syndrome (AIDS).

It has previously been demonstrated that gonadal insufficiency may occur in some men with HD prior to treatment²⁴. The present results indicate that an impaired gonadal function is especially common in a subgroup of men with HD or NHL for whom the etiology is entirely unknown. Because sex hormones may modulate immune responses¹² further studies of the possible relation between gonadal function and malignant lymphoma are warranted.

REFERENCES

1. Vianna N J, Polan A. Lymphomas and occupational benzene exposure. *Lancet* 1979; i:1394-95.
2. Olsson H, Brandt L. Occupational exposure to organic solvents and Hodgkin's disease in men. A case-referent study. *Scand J Work Environ Health* 1980; 302-05.
3. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphomas and exposure to chemical agents, especially to organic solvents, chloro-phenols and phenoxy acids. A case-control study. *Br J Cancer* 1981; 43: 169-76.
4. Ross R, Nichols P, Wright W, Lukes R, Dworsky R, Paganini-Hill A, Koss M, Henderson B. Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. *Lancet* 1982; ii:1118-20.
5. Thorell J I, Larsson S M. Radioimmunoassay and related techniques. Saint Louis: C V Mosby Co., 1978; 147-58.
6. Rappaport H. Tumors of the hematopoietic system. In: *Atlas of Tumor Pathology*. Section 3, Fasc. 8. Washington D.C. Armed Forces Institute of Pathology, 1966; 1-442.
7. Rosenberg S A. Report of the committee on the staging of Hodgkin's disease. *Cancer Res* 1966; 26: 1310.
8. Carbone P P, Kaplan H S, Musshof K, Smithers D W, Tubiana M. Report of the committee on Hodgkin's disease staging. *Cancer Res* 1971; 31: 1860-61.
9. Greene M H. Clinical and predisposing factors. In: Berard C W, mod. *A multidisciplinary approach to non-Hodgkin's lymphomas*. NIH Conference. *Ann Intern Med* 1981; 94: 218-35.
10. Renard P, Celers J. Viral infections with urogenital manifestations. In: Debré R, Celers J, eds. *Clinical Virology*. Philadelphia: W B Saunders Co, 1970; 705-14.

11. Lang D J, Kummer J F. Demonstration of cytomegalovirus in semen. *N Engl J Med* 1972; 287: 756-58.
12. Talal N. ed. Proceedings of the Kroc Foundation Conference on sex factors, steroid hormones, and the host response. *Arthrit Rheum* 1979; 22: 1153-98.
13. Gershwin M E, Steinberg A D. Loss of suppressor function as a cause of lymphoid malignancy. *Lancet* 1973; ii:1174-76.
14. Steinberg A D, Melez K A, Raveche E S, Reeves J P, Boegel W A, Smathers P A, Taurog J D, Weinlein L, Duvic M. Approach to the study of the role of sex hormones in autoimmunity. *Arthritis Rheum* 1979; 22: 1170-76.
15. Roubinian J, Talal N, Siiteri P, Sadakian J A. Sex hormone modulation of autoimmunity in NZV/NZW mice. *Arthritis Rheum* 1979; 22: 1162-69.
16. Louie S, Daoust P R, Schwartz R S. Immunodeficiency and the pathogenesis of non-Hodgkin's lymphoma. *Semin Oncol* 1980; 7: 267-84.
17. Mc Farlin D E, Strober W, Waldmann T A. Ataxia-teleangiectasia. *Medicine* 1972; 51: 281-314.
18. Spector B D, Perry G S, Kersey J H. Genetically determined immunodeficiency diseases (GDID) and malignancy: Report from the Immunodeficiency-Cancer Registry. *Clin Immunol Immunopathol* 1978; 11: 12-16.
19. Kolodny R C, Jacobs L S, Masters W H, Hendryx J. Plasma testosterone and semen analysis in male homosexuals. *N Engl J Med* 1971; 285: 1170-74.
20. Kolodny R C, Jacobs L S, Masters W H, Toro G, Daughady W H. Plasma gonadotrophins and prolactin in male homosexuals. *Lancet* 1972; ii:18-20.
21. Doerr P, Kockott G, Vogt H J, Pirke K, Dittmar F. Plasma testosterone, estradiol and semen analysis in male homosexuals. *Arch Gen Psychiatr* 1973; 29: 829-33.

22. Brodie H K H, Gartrell N, Doering C, Rhue T. Plasma testosterone levels in heterosexual and homosexual men. *Am J Psychiatr* 1974; 131: 82-83.
23. Metroka C E, Cunningham-Rundles S, Pollack M, Sonnabend J A, Davis J M, Gordon B, Fernandez R D, Mouradian J. Generalized lymphadenopathy in homosexual men. *Ann Intern Med* 1983; 99: 585-91.
24. Vigersky R A, Chapman R M, Berenberg J, Glass A. Testicular dysfunction in untreated Hodgkin's disease. *Am J Med* 1982; 73: 482-86.

LOW FERTILITY PRIOR TO THERAPY IN A SUBGROUP OF MEN WITH MALIGNANT LYMPHOMA

Håkan Olsson¹ and Jonas Ranstam²

¹Department of Oncology, ²Southern Swedish Regional Tumour Registry,
University Hospital, S-221 85 Lund, Sweden

SUMMARY

Lifetime occupational histories were obtained from 150 men with a recent diagnosis of non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD) and the number of children fathered by each patient was recorded. Prolonged occupational exposure to organic solvents, exposure to phenoxy acids or therapeutic irradiation had occurred in 72 patients and according to published epidemiological data it was considered that exposure to environmental hazards was of etiologic importance for some of these patients. For 78 patients no pronounced exposure to such agents was recorded and other as yet unidentified etiologic factors were assumed to be more important for these patients. The proportion of childless patients (40 %) was significantly larger in the unexposed group than in the group of exposed patients (18 %). The number of children per individual was significantly lower in the unexposed than in the exposed patients, 1.24 and 2.13 respectively. The fertility of unexposed lymphoma patients was also significantly lower than in a reference group of 138 men with bladder cancer and in another reference group of 198 men with acute medical illness. The fertility of exposed lymphoma patients and of the two reference groups was not significantly different.

The results are in agreement with previous results indicating a relatively impaired testicular function in a subgroup of male lymphoma patients for whom the etiology of the lymphoproliferative disease is entirely unknown. As yet unidentified agents may impair the gonadal function in men and may also be of etiologic importance for their lymphoproliferative malignancy. Alternatively, men with a congenital or acquired impairment of the testicular function may constitute a risk group for malignant lymphoma.

INTRODUCTION

Results of epidemiological studies suggest that exposure to various environmental agents are of etiologic importance for some patients with malignant lymphoma. Thus occupational exposure to organic solvents (1, 2, 3), handling of phenoxy acids and chlorophenols (3), asbestos exposure (4), and exposure to ionizing irradiation (5) may constitute risk factors. For other lymphoma patients no pronounced exposure to such environmental factors is obvious and other as yet unidentified risk factors are likely to be more important. In a previous study various clinical and biochemical characteristics were analysed in a group of male lymphoma patients with a heavy exposure to organic solvents and in another group without any known

prolonged exposure to such agents (6). Differences in sex hormone levels and semen characteristics suggested that the exposed patients had an essentially normal testicular function whereas the patients with malignant lymphoma of entirely unknown etiology had signs of an impaired gonadal function. In the present study the fertility to diagnosis has been assessed in a group of male lymphoma patients exposed to agents which, according to epidemiological evidence, might favour the development of malignant lymphoma and in patients for whom other, as yet unknown factors are likely to be more important.

MATERIAL

Patients

A total of 150 consecutive men with malignant lymphoma (99 with non-Hodgkin's lymphoma (NHL), median age 57; range 26-81 yrs and 51 patients with Hodgkin's disease (HD), median age 36; range 18-78 yrs) seen at the Department of Oncology, University Hospital, Lund, Sweden, were included in the study.

The patients are admitted from an area with a population of 1.2 million inhabitants, covering the southern region of Sweden except the city of Malmö. Thus approximately 70 % of the eligible patients in the region with lymphoma are admitted to our clinic. Very old and very sick patients are less often referred. To our knowledge there is no socio-economic selection of the patients. All diagnoses are based on adequate biopsy material examined by pathologists with a special interest in malignant lymphoma. Biopsies taken at other hospitals are reexamined. For histological diagnosis the Rappaport (7) or the Rye classification (8) are used. The Ann Arbor system (9) is used for staging of the lymphomas. The patient material is presented in Table I. The lymphoma patients were interviewed during 1979 and 1980.

Table I. Histology and stage in patients with NHL and HD

NHL histology	No.
Diffuse well-differentiated lymphocytic	7
Nodular well-differentiated lymphocytic	2
Diffuse poorly differentiated lymphocytic	24
Nodular poorly differentiated lymphocytic	12
Diffuse mixed	8
Nodular mixed	8
Diffuse histiocytic	29
Nodular histiocytic	1
Lennert lymphoma	2
Undifferentiated lymphoma	3
Unclassifiable	3

NHL stage	No.
I	23
II	13
III	19
IV	25
Extranodal	19

HD histology	No.
Nodular sclerosis	28
Mixed cellularity	19
Lymphocytic predominance	4
Lymphocytic depletion	0

HD stage	No.
I A	17
I B	0
II A	10
II B	3
III A	9
III B	5
IV A	2
IV B	5

Referents

Two referent materials were analysed. One group comprised 138 consecutive men with bladder cancer seen at the Departments of Oncology and Urology, University Hospital, Lund, during 1980 to 1983. The median age of the patients was 64 yrs, range 26-84. The patients were living in the same geographical region as the lymphoma patients. Another group of 198 men with acute medical illness seen at the Department of Internal Medicine, University Hospital, Lund, during 1981 was also studied. The median age was 60 yrs (range 30-83) and most of the patients were living in the vicinity of the hospital.

METHODS

Occupational history

In each lymphoma patient a lifetime occupational history was taken as described previously (2). Exposure to organic solvents, herbicides and therapeutic exposure to ionizing irradiation was recorded. Patients who had handled organic solvents for at least one year each working day prior to diagnosis were considered exposed to solvents. Patients who had ever handled herbicides occupationally in the form of phenoxy acids were considered exposed to such agents and patients who had received therapeutic irradiation for benign or other malignant diseases were classified as exposed to ionizing radiation.

Fertility history

The lymphoma patients and the referents were questioned in a structured interview about number and year of birth of all the children they had fathered. Stillbirths were included while abortions were excluded.

Statistical methods

Chi-square tests were used in univariate, unstratified analyses. When the material was stratified the Mantel-Haenszel chi-square test was employed. To control for interdependencies in the material mathematical modelling by covariance-, regression-, logistic regression-, and discriminant analysis was performed. All tests were two-tailed.

RESULTS

The 150 men with malignant lymphoma were grouped according to the type of exposure. Forty-eight patients had been exposed to organic solvents only.

A combined exposure to organic solvents and herbicides occurred in four patients and to organic solvents and therapeutic irradiation in six patients. Herbicide exposure was the single exposure recorded in thirteen patients, while herbicide exposure and exposure to therapeutic irradiation had occurred in two patients. Five patients had a history of therapeutic irradiation as the only exposure. Seventy-two patients were considered unexposed to the agents mentioned (Table II). There was no significant difference in average age between the exposed and unexposed groups. Fifty per cent of the patients with HD and fifty-three per cent of the patients with NHL were unexposed.

Fertility in unexposed and exposed patients

Forty per cent of the unexposed patients were childless compared to eighteen per cent of the exposed patients (Table II). The difference is significant after controlling for age at diagnosis ($p < 0.001$). In the unexposed group the average number of children was 1.24 per patient and in the exposed group 2.13. The difference is significant after adjustment for age ($p < 0.0001$). Among the unexposed patients who had fathered children, fertility was lower than in the exposed patients with children ($p < 0.03$). Correction for type of lymphoma (NHL, HD) did not change the findings of a lower fertility in the unexposed patients.

Fertility in the unexposed group was also compared to fertility in sub-groups of exposed patients. The proportion of childless patients was larger and the average number of children per patient lower in the unexposed group than in 58 patients exposed to organic solvents ($p < 0.003$ and $p < 0.0001$ respectively). The proportion of childless patients was larger in the unexposed patients when compared to the 15 patients exposed to herbicides ($p < 0.07$). In this analysis the patients with a combined exposure to organic solvents and herbicides were excluded.

It was considered possible that exposure to certain chemicals might be associated with an increased fertility and that the different fertility in exposed and unexposed men was due to such exposure. To evaluate this possibility a matched analysis was performed. For each of the 58 patients exposed to solvents the unexposed patient closest in age was selected for comparison. The age when exposure began was recorded for each exposed patient and fertility before and after the beginning of exposure was recorded. For each matched unexposed patient fertility was recorded in

the same period. The results of this comparison are shown in Fig 1. As can be seen exposure did not significantly influence fertility nor affect the difference, even prior to exposure, in number of children between the two groups. Among the solvent-exposed patients 129 children were born compared to 80 children among the unexposed men (X^2 , $p < 0.02$). Stratifying the material in NHL and HD did not influence the finding.

Comparison of fertility in lymphoma patients and referents

The proportion of childless patients was 29 % in the lymphoma group and 18 % in the patients with bladder cancer ($0.1 < p < 0.2$ after adjusting for age at diagnosis). The average number of children in the whole group of lymphoma patients was 1.70 and in the patients with bladder cancer 1.95. The difference is not significant ($p > 0.2$).

In the subgroup of unexposed lymphoma patients the proportion of childless patients was 40 % and significantly larger than among the patients with bladder cancer ($p < 0.001$). Unexposed lymphoma patients had 1.24 children per individual. The number is significantly lower than 1.95 recorded in the patients with bladder cancer ($p < 0.004$).

In the group of 78 exposed lymphoma patients and in the patients with bladder cancer the proportion of childless patients and the number of children per patient were not significantly different when controlling for age at diagnosis of the malignant disorder ($p > 0.2$).

The fertility of 127 lymphoma patients aged ≥ 30 years was also compared with the fertility of the patients with acute medical illness (Table III).

In the total group of patients with lymphoma and in the referent group the proportion of childless men was similar and the number of children per patient was not significantly different in the two groups after adjusting for age at examination. However, the unexposed lymphoma patients were more often childless than the referents with acute medical illness ($p < 0.03$) and the solvent-exposed lymphoma patients had significantly more children, on the average 2.28 compared to 1.74 among the medical patients ($p < 0.02$).

Table II. Fertility in different exposure groups

	Patients (no.)	Average age (yrs)	Average no. of children	Ratio of men without children (%)
Exposed lymphoma patients				
Solvents	48	49.4	2.21	7/48 (15)
Solvents and herbicides	4		2.25	1/4
Solvents and irradiation	6		2.33	0/6
Herbicides	13	59.6	2.38	2/13 (15)
Herbicides and irradiation	2		0	2/2
Irradiation	5		1.20	2/5
Total exposed patients	78	51.1	2.13	14/78 (18)
Unexposed lymphoma patients	72	49.6	1.24	29/72 (40)

Table III. Fertility in lymphoma patients and referents

	Patients (no.)	Average no. of children	Ratio of men without children (%)
Lymphoma patients (all)	150	1.70	29
Lymphoma patients (≥ 30 yrs)			
Solvent exposed	52	2.28	16
Herbicide exposed	13	2.38	15
Unexposed	62	1.39	33
Total	127	1.79	24
Bladder cancer patients	138	1.95	18
Acute medical patients (≥ 30 yrs)	198	1.74	20

Number of children

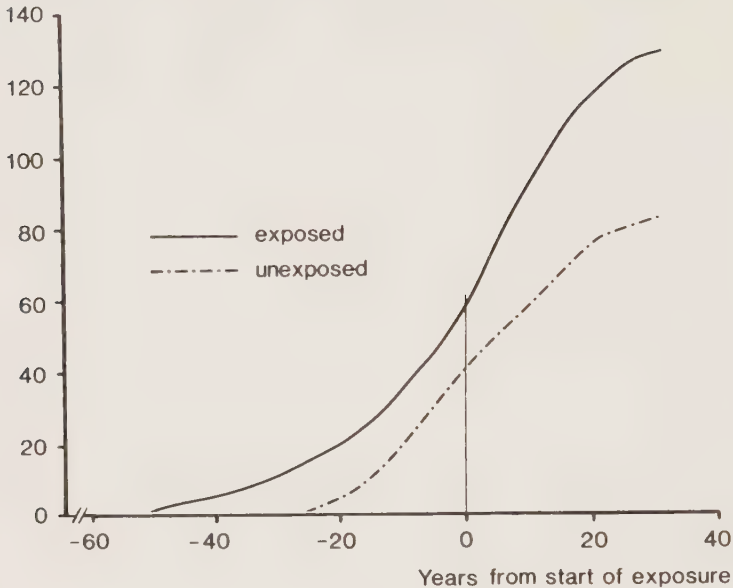


Fig 1. Cumulative number of children is shown in relation to exposure status of the father. The start of the exposure is indicated with a vertical line. A paired, age-matched, child-oriented analysis has been performed giving the unexposed patient the same starting point of the exposure as the exposed matched counterpart.

DISCUSSION

In the present investigation, fertility was evaluated in two groups of men with a recent diagnosis of malignant lymphoma. One group comprised men for whom a thorough interview did not reveal any pronounced exposure to environmental hazards proposed as risk factors for malignant lymphoproliferative disorders (1, 2, 3, 4, 5). Another group comprised men for whom such exposure was evident. It was considered probable that for some patients in this group exposure to chemicals or ionizing radiation was of etiologic importance for their diseases. For most of the 'unexposed' patients other, yet unidentified etiologic factors were assumed to be more important.

Among the unexposed patients, fertility was significantly lower than in the exposed group. A matched analysis of unexposed patients and patients occupationally exposed to organic solvents revealed that the exposed

patients were more fertile than the unexposed patients before and after the beginning of exposure. Thus the difference in fertility between unexposed and exposed patients was apparently not due to an enhanced fertility associated with exposure and it was considered probable that a relatively low fertility may be characteristic for men with malignant lymphoma of unknown etiology.

A comparison of the fertility in lymphoma patients and in a referent group of men with a recent diagnosis of another malignant disease, bladder cancer, supported the view that unexposed lymphoma patients have a subnormal fertility. Thus the number of childless patients was larger and the number of children per individual was lower in the unexposed lymphoma patients than in the group of patients with bladder cancer. There was no significant difference in fertility between exposed lymphoma patients and the referents with a bladder cancer.

The fertility in men with lymphoma was also compared with the fertility in a referent material of patients with acute medical illness. Because many of these referents had diseases that possibly reduced their desire or ability to father children a relatively low fertility might be expected in this group. Nevertheless, the proportion of childless patients was larger in the unexposed lymphoma patients than in the patients with acute medical illness.

The finding of a low fertility in a subgroup of men with lymphoma of unknown etiology is in agreement with previous results of sex hormone analyses and sperm tests in men with malignant lymphoma. We have found that among men with lymphoma following prolonged exposure to organic solvents the levels of P-testosterone and S-luteinizing hormone are essentially normal. Moreover, the concentration of sperm cells in semen was found to be normal in this group. In another group of men for whom other, as yet unidentified factors are probably of greater etiologic importance, signs of an impaired gonadal function were more common (6).

In brief, our previous results of sex hormone analyses and sperm tests together with the present findings strongly suggest that a reduced gonadal function may be characteristic of a subgroup of men with malignant lymphoma. The impaired testicular function may be caused by as yet unidentified agents which may also be of etiologic importance for the development of lymphoproliferative malignancies. Alternatively a reduced gonadal function,

hereditary or acquired, may constitute a risk factor for malignant lymphoma in men.

REFERENCES

1. Vianna N.J., Polan A. Lymphomas and occupational benzene exposure. *Lancet* 1979; 1394-1395.
2. Olsson H., Brandt L. Occupational exposure to organic solvents and Hodgkin's disease in men. A case-referent study. *Scand J Work Environ Health* 1980; 302-305.
3. Hardell L., Eriksson M., Lenner P., Lundgren E. Malignant lymphomas and exposure to chemical agents, especially to organic solvents, chlorophenols and phenoxy acids. A case-referent study. *Br J Cancer* 1981; 43: 169-176.
4. Ross R., Nichols P., Wright W., Lukes R., Dworsky R., Paganini-Hill A., Koss M., Henderson B. Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. *Lancet* 1982; ii: 1118-1120.
5. Greene M. Non-Hodgkin's lymphoma and Mycosis Fungoides. In *Cancer Epidemiology and Prevention*. Editors: Schottenfeld D., Fraumeni J.F. W.B. Saunders, Philadelphia. 1982: 754-778.
6. Olsson H., Brandt L., Ranstam J., Bjerström M. Impaired testicular function in a subgroup of men with malignant lymphoma. (Submitted for publication.)
7. Rappaport H. Tumors of the Hematopoietic system. In: *Atlas of Tumor Pathology*. Section 3, Fasc. 8. Washington D.C. Armed Forces Institute of Pathology, 1966; 1-442.
8. Rosenberg S.A. Report of the committee on the staging of Hodgkin's disease. *Cancer Res* 1966; 26: 1310.
9. Carbone P.P., Kaplan H.S., Musshof K., Smithers D.W., Tubiana M. Report of the committee on Hodgkin's disease staging. *Cancer Res* 1971; 31: 1860-1861.

LATE AGE AT FIRST FULL TERM PREGNANCY
AS A RISK FACTOR FOR WOMEN
WITH MALIGNANT LYMPHOMA

Håkan Olsson¹, Mona Landin Olsson² and Jonas Ranstam³

¹Department of Oncology, University Hospital, S-221 85 Lund, Sweden,

²Department of Internal Medicine, Malmö General Hospital, S-214 01 Malmö, Sweden, ³Southern Swedish Regional Tumour Registry, University Hospital,

S-221 85 Lund, Sweden

SUMMARY

Women with malignant lymphoma, non-Hodgkin's lymphoma and Hodgkin's disease, were of a significantly later age at first full-term pregnancy (AFFP) than controls without malignant disorders. The odds ratio of having the first pregnancy at 30 years of age was 6.4 for women with malignant lymphoma. This ratio was higher than the ratio of 3.9 in a group of breast cancer patients. A low parity in the lymphoma group enhanced the risk associated with a late AFFP.

INTRODUCTION

Results of analyses of the gonadal function (1, 2) and the reproductive history (3) in men with malignant lymphoma suggest that a decreased fertility prior to diagnosis is characteristic of a subgroup of the patients. For women it has been found that a low parity is associated with an increased risk of Hodgkin's disease (4) suggesting that also in women the reproductive history may have some bearing on the development of malignant lymphoproliferative disorders.

In the present investigation, the age at first full term pregnancy (AFFP) and the number of children were recorded in a group of women with a recent diagnosis of malignant lymphoma and in control groups. Females without known malignant disorders constituted one reference group. Another reference group comprised patients with breast cancer because a late AFFP is associated with an increased risk of this disease (5). Our data indicate that a late AFFP is also unduly common in women with malignant lymphoma.

MATERIALS AND METHODS

Patients with malignant lymphoma

One hundred and seventeen patients with biopsy proven malignant lymphoma were interviewed 1980-1982 about AFFP and parity. Seventy-nine had non-Hodgkin's lymphoma (NHL) and 38 Hodgkin's disease (HD). The material comprises consecutive patients seen at the Department of Oncology, University Hospital, Lund, where diagnosis and treatment of lymphoma in the southern region of Sweden, except the city of Malmö, is centralized. Approximately 70 % of the eligible patients in the region come to the hospital. No patients were excluded from interview. The age distribution is given in Table I.

Patients with thyreotoxicosis

Ninety-eight consecutive female patients with thyreotoxicosis referred to the Department of Oncology for radio-iodine treatment were interviewed during 1982. The age distribution is given in Table I.

Patients with acute medical illness

During 1981-1982, 172 consecutive women with acute medical illness seen at the Emergency Department, University Hospital, Lund, were interviewed about AAFP and parity. Eighteen patients were excluded from interview because of severe illness. The age distribution is given in Table I.

Outpatient controls

One hundred and eighty-eight women seen at Dalby Community Health Research Center, Dalby, Sweden, were interviewed during 1980. The center is a primary care facility for basic population research where health check-ups are performed and primary care is given. No patients were excluded from interview. The age distribution is given in Table I.

Patients with breast cancer

One hundred and seventy-three patients with breast cancer were interviewed about AAFP and parity. The material comprises consecutive patients seen at the Department of Oncology, University Hospital, Lund, during two periods 1980 and 1982. Among the patients referred to the clinic, where both radiotherapy and chemotherapy are given, a large proportion had stage II disease (60 %) and minor proportions stage I (15 %) and stages III-IV (25 %). There is no socio-economic selection of patients. For age distribution, see Table I.

Statistical methods

Analysis of variance and chi-square tests were used in univariate analysis. Multivariate analyses were performed in order to control for age at diagnosis and parity through linear and logistic regression models. Relative risks were estimated by odds ratios (OR); 95 % confidence intervals (CI) and two-tailed p-values were calculated. Statistical significance refers to p-values less than 5 %.

Table I. Number of subjects and average age (range) of each group of patients

Diagnosis	No.	Average age, yrs (range)
Malignant lymphoma	117	50.0 (17-85)
Thyreotoxicosis	98	56.1 (30-81)
Acute medical illness	172	52.5 (15-86)
Outpatient controls	188	39.9 (18-83)
Breast cancer	173	57.3 (27-80)

RESULTS

Age at first full-term pregnancy (AFFP) as a risk factor

In an analysis of the three reference groups without malignant disorders, i.e. women with thyreotoxicosis, women with acute medical illness and outpatient controls, it was found that older patients had a later AFFP than younger ones ($p < 0.003$). In the calculation of AFFP in the various groups studied an adjustment for age at interview was therefore performed. The adjusted AFFP values are given in Table II. In the lymphoma patients the average AFFP was 26.1 years. In the control groups of women without malignancy the average AFFP was 24.6, 24.0 and 24.9 respectively. Breast cancer patients had an AFFP of 25.6 years. In order to evaluate AFFP as a possible risk factor for malignant lymphoma the lymphoma patients were compared with the controls without malignant disorders. In these analyses patients with thyreotoxicosis, acute illness and outpatient controls constituted one reference group. The pooling of these three subgroups was considered justified because AFFP was not significantly different in the groups. The results are shown in Table III. Malignant lymphoma was significantly associated with a late AFFP ($p < 0.005$). If a late AFFP, 30 years, is selected as a point for the estimation of risk for women with malignant lymphoma compared to the controls the odds ratio is 6.4. The ratio for NHL patients is 7.2 ($p < 0.006$) and for HD 4.8 ($p < 0.16$).

Corresponding comparisons were performed between the breast cancer patients and the controls. As expected, an association between breast cancer and AFFP was found ($p < 0.02$) and the odds ratio for an AFFP at 30 years of age

was 3.9. Thus a late AAFP seems to be an even stronger risk factor for malignant lymphoma than for breast cancer (Table III).

Parity as risk factor

Parity was analysed in the lymphoma group and in the reference groups without malignant disease. Because there were no significant differences between the various reference groups regarding nulliparity and average number of children, the three groups were pooled.

Nulliparity and the number of children per individual were related to the age at examination of the lymphoma patients and the combined control group, i.e. young patients were more often nulliparous than older patients. The average number of children was also lower in young patients compared to older ones. The proportion of nulliparous patients and the average number of children were therefore adjusted for the age at examination. Parity in the lymphoma group, the combined control group and the group of breast cancer patients is shown in Table IV. There were no significant differences between the groups of patients. However, the lowest average number of children was observed in the lymphoma group. There was no significant difference between NHL and HD patients in regard to AAFP, percentage of nulliparous women and the average number of children per individual.

The combination of a late AAFP and a low parity as a risk factor

Because a late AAFP was found to be a strong risk factor for malignant lymphoma and the average number of children was seemingly low in the lymphoma patients it was considered possible that women with a late AAFP and with a low parity are more prone to develop malignant lymphoma than those who begin their reproductive period early and give birth to many children. To test this hypothesis women with an AAFP of 20 years or less who had borne 3 or more children were used as a reference group with an OR of 1.00. For women with ≥ 3 children there was an apparent increase in OR associated with an increasing AAFP. A similar pattern was observed for those who had given birth to 1-2 children. However, the OR at various AAFP were always higher for women with 1-2 children than for those with ≥ 3 children. The highest OR was observed for a group of women with AAFP of 30 years or older who had 1-2 children (Table V). Apparently women with a combination of a late AAFP and a low parity are at special risk of developing malignant lymphoma.

Table II. Average age at first full term pregnancy,
adjusted for age at examination

Diagnosis	AFFP (yrs)
Malignant lymphoma	26.1
Thyreotoxicosis	24.6
Acute medical illness	24.0
Outpatient controls	24.9
Breast cancer	25.6

Table III. AFFP as a risk factor in patients with malignant lymphoma (HD and NHL) and breast cancer in relation to a combined control group of women with thyreotoxicosis, acute medical illness and outpatient controls. Logistic regression. P-value for the coefficient and point estimate of the risk for a woman to have her AFFP at 30 years of age is shown. Age adjusted analysis.

Diagnosis	Logistic regression		Risk at 30 years of age	
	P-value	Coefficient	OR	95 % CI
Malignant lymphoma	0.005	0.062	6.4	1.7-24.0
Hodgkin's disease	0.16	0.052	4.8	0.6-41.3
Non-Hodgkin's lymphoma	0.006	0.066	7.2	1.7-30.6
Breast cancer	0.02	0.045	3.9	1.2-12.8

Table IV. Percentage of nulliparous women and number of children per individual in lymphoma patients and reference patients. Adjusted for age at examination.

Diagnosis	Nulliparous (%)	Average no. of children
Hodgkin's disease	27	1.62
Non-Hodgkin's lymphoma	18	1.66
Combined control group	23	1.88
Breast cancer	25	1.77

Table V. AAFP and parity in women with malignant lymphoma compared with a combined group of referents. The odds ratio (OR) is given in relation to the women with a parity of ≥ 3 children and a AAFP ≤ 20 years.

AAFP	Parity (OR, 95 % CI, p-value)					
	1-2 children			≥ 3 children		
	OR	95 % CI	p-value	OR	95 % CI	p-value
≤ 20 yrs	1.42	0.58-1.25	0.44	1.00	-	-
21-29 yrs	2.07	0.98-1.47	0.05	1.74	0.80-1.34	0.16
≥ 30 yrs	2.48	1.15-5.35	0.02	2.14	0.85-5.36	0.10

DISCUSSION

The results of the present study indicate that a late AAFP is a risk factor for malignant lymphoma. The relation between a late AAFP and lymphoma was especially strong among 79 patients with NHL. In these patients an AAFP of 30 years was associated with an OR of 7.2. In HD this OR was lower, 4.8, and did not reach statistical significance, possibly because a relatively low number of women, 38, had HD. It was also found that the risk of developing malignant lymphoma is especially high if a late AAFP is combined with a low fertility.

Different socio-economic or geographical conditions might be of importance for differences in reproductive histories. However, the lymphoma patients and the controls were living in a region of southern Sweden with about 1.2 million inhabitants and with a uniform health care system. There was a small difference in the geographical origin between the lymphoma patients, who were admitted from the whole region, and the reference group of women with acute medical illness and the outpatient control group who lived in the vicinity of our hospital. However, a third reference group of patients with thyreotoxicosis admitted for treatment with ^{131}I came from the whole region, as did the lymphoma patients, and this reference group had a lower AAFP than the lymphoma patients. Moreover, their AAFP did not differ from the referents living near our hospital. It is therefore unlikely that the small differences in geographical origin were of any significant importance for the differences in reproductive patterns between lymphoma patients and reference patients.

The patients with NHL and HD had a relatively low average number of children, although the finding was not statistically significant. HD is more common in families with small sibships than in larger families (6). It has been proposed that HD is more common in high social classes than in lower classes (7, 8). Gutensohn and Cole (6) have pointed out that family size is a social class indicator. Hence it may be that social class is more pertinent than family size. However, in more recent studies no relation between a high social class and an increased risk of HD was observed (9). The elevated risk for HD in small families may therefore be associated with a low reproductive capacity rather than with socio-economic factors.

The mechanisms bringing about an association between the reproductive history and the development of lymphoma in women are unknown. Because most patients became ill after the cessation of their reproductive period, it is unlikely that their late AFFP and seemingly low parity were caused by the lymphoproliferative disease. The mechanisms of importance for the relation between the reproductive pattern and lymphoma were probably operating prior to the development of symptoms of a lymphoproliferative malignancy. Estrogen stimulation by ovulatory cycles may be especially pronounced in females with a late AFFP and a low number of pregnancies. Such stimulation has been proposed as relevant for the association between a late AFFP and breast cancer (10). It is possible that a frequent estrogen stimulation may also be of importance for the development of malignant lymphoma. In experimental studies of irradiated mice it has been found that estrogen treatment favours the development of lymphoid tumours whereas androgen treatment is followed by myeloid malignancies (11). NZB mice are prone to develop autoimmune disorders and malignant lymphoma (12). In these animals estrogen treatment causes a reduction of thymus weight and aggravates the symptoms of autoimmunity (12). However, estrogen treatment has not, to our knowledge, been associated with any increased risk of malignant lymphoma in man.

Interestingly, a late AFFP was an even stronger risk factor for malignant lymphoma than for breast cancer and a low parity seemed to reinforce this risk. Previous studies of the gonadal function (1, 2) and reproductive history (3) in men with malignant lymphoma have indicated that the fertility is subnormal prior to diagnosis in a subgroup of the patients. According to the present results, certain characteristics in the reproductive history of females may also have some bearing on the development of malignant lymphoma.

REFERENCES

1. Olsson H., Brandt L., Ranstam J., Bjerström M. Impaired testicular function in a subgroup of men with malignant lymphoma. (Submitted for publication.)
2. Vigersky R.A., Chapman R.M., Berenberg J., Glass A. Testicular dysfunction in untreated Hodgkin's disease. *Am J Med* 1982; 73: 482-486.
3. Olsson H., Ranstam J. Low fertility prior to therapy in a subgroup of men with malignant lymphoma. (Submitted for publication.)
4. Abramson J.H., Pridon H., Sacks M.I., Avitzour M., Peritz E. A case-control study of Hodgkin's disease in Israel. *J Natl Cancer Inst* 1978; 61: 307-314.
5. Vorherr H. Breast cancer. Urban & Schwarzenberg. Baltimore-Munich. 1980; 55-80.
6. Gutensohn N., Cole P. Epidemiology of Hodgkin's disease in the young. *Int J Cancer* 1977; 19: 595-694.
7. LeShan L., Marvin S., Lysterly O. Some evidence of a relationship between Hodgkin's disease and intelligence. *Arch Gen Psychiatry* 1959; 1: 477-479.
8. Mac Mahon B. Epidemiology of Hodgkin's disease. *Cancer Res* 1966; 26: 1189-1200.
9. Grufferman S. Hodgkin's disease. In *Cancer Epidemiology and Prevention*. Eds: Schottenfeld D., Fraumeni J.F. W.B. Saunders. Philadelphia. 1982; 739-753.
10. Cole P., Mac Mahon B. Oestrogen fractions during early reproductive life in the etiology of breast cancer. *Lancet* 1969; 1: 604-606.
11. Duplan J.F. Neoplasms of hematopoietic systems. In *Scientific Foundations of Oncology*. Ed: Symington T., Carter R.L. William Heinemann Medical Books Ltd. London. 1976; 444-456.

12. Steinberg A.D., Melez K.A., Raveche E.S., Reeves J.P., Boegel W.A., Smathers P.A., Taurog J.D., Weinlein L., Duvic M. Approach to the study of the role of sex hormones in autoimmunity. *Arthritis Rheum* 1979; 22: 1170-1176.

